



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US98/17563  (22) International Filing Date: 25 August 1998 (25.08.98)  (30) Priority Data: 60/056,963 26 August 1997 (26.08.97) US 60/057,932 4 September 1997 (04.09.97) US  (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications US 60/056,963 (CON) Filed on 26 August 1997 (26.08.97) US 60/057,932 (CON) Filed on 4 September 1997 (04.09.97)  (71) Applicants (for all designated States except US): BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM [US/US]; 201 West Seventh Street, Austin, TX 78701 (US). WAKE FOREST UNIVERSITY [US/US]; Medical Center Boulevard, Winston-Salem, NC 27157-1023 (US).  (72) Inventors; and (75) Inventors/Applicants (for US only): RAAID, Issam [US/US]; 7615 Del Rey Lane, Houston, TX 77071 (US). SHERERTZ,		Robert [US/US]; 3417 Jameson Lane, Winston-Salem, NC 27106 (US).  (74) Agent: BOWLES, Teresa, J.; Arnold, White & Durkee, P.O. Box 4433, Houston, TX 77210 (US).  (81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.																					
(54) Title: CHELATORS IN COMBINATION WITH BIOCIDES: TREATMENT OF MICROBIALY INDUCED BIOFILM AND CORROSION																							
<table border="1"> <caption>Data points estimated from the graph</caption> <thead> <tr> <th>Time (h)</th> <th>Am B</th> <th>E (1mg/mL)</th> <th>A + E (1)</th> <th>Control</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>4.0</td> <td>4.0</td> <td>4.0</td> <td>4.0</td> </tr> <tr> <td>24</td> <td>4.4</td> <td>4.0</td> <td>2.4</td> <td>5.9</td> </tr> <tr> <td>48</td> <td>5.1</td> <td>3.3</td> <td>2.1</td> <td>6.8</td> </tr> </tbody> </table>				Time (h)	Am B	E (1mg/mL)	A + E (1)	Control	0	4.0	4.0	4.0	4.0	24	4.4	4.0	2.4	5.9	48	5.1	3.3	2.1	6.8
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(57) Abstract  Control of biofouling in pipes or aqueous systems via the use of compositions and methods that include the combination of a chelator with an antimicrobial agent, such as EDTA with Amphotericin B, this particular combination shown to synergistically inhibit <i>Aspergillus fumigatus</i> in the figure.																							

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## DESCRIPTION

### CHELATORS IN COMBINATION WITH BIOCIDES: TREATMENT OF MICROBIAALLY INDUCED BIOFILM AND CORROSION

#### BACKGROUND OF THE INVENTION

##### **1. Field of the Invention**

This invention relates to a method for controlling biofouling in a variety of applications including water treatment, pulp and paper manufacture and oil field water flooding. More specifically, this invention relates to a method for controlling biofouling with a combination of  
5 an antifungal or antibiotic and a chelator.

##### **2. Description of Related Art**

Biological fouling on surfaces is a serious economic problem in many commercial and industrial aqueous process and water handling systems. For example, in 1993 North American  
10 companies spent \$1.2 billion on water treatment chemicals alone to fight corrosion and fouling caused by microbial organisms embedded in biofilm attached to the surfaces of pipelines. Fouling comprises a biomass which is the buildup of microorganisms and/or extracellular substances, as well as dirt or debris that become trapped in the biomass. Bacteria, fungi, yeasts, diatoms and protozoa are only some of the organisms which cause buildup of a biomass. If not  
15 controlled, the biofouling caused by these organisms can interfere with process operations, lower the efficiency of processes, waste energy and reduce product quality.

Cooling water systems used in power-generating plants, refineries, chemical plants, air conditioning systems and other commercial and industrial operations frequently encounter  
20 biofilm problems. This is because cooling water systems are commonly contaminated with airborne organisms entrained by air/water contact in cooling towers, as well as waterborne organisms from the systems' makeup water supply. The water in such systems is generally an excellent growth medium for these organisms. If not controlled, the biofilm biofouling resulting from such growth can plug towers, block pipelines and coat heat transfer surfaces with  
25 layers of slime, and thereby prevent proper operation and reduce equipment efficiency. Furthermore, significant increases in frictional resistance to the flow of fluids through conduits

affected by biofouling results in higher energy requirements to pump these fluids. In secondary oil recovery, which involves water flooding of the oil-containing formation, biofilms can plug the oil-bearing formation.

5 Perhaps most significantly from an economic point of view, it has recently been demonstrated that biofilms adhering to stainless steel and other metal pipeline surfaces can shift the open circuit potential of the metal, thereby accelerating the propagation rate of corrosion. Although biofilms can contain any type of microorganism, including algae, fungi and both aerobic and anaerobic bacteria, these films are often comprised of sulfate-reducing bacteria  
10 which grow anaerobically in water, frequently in the presence of oil and natural gases. Colonies that include several kinds of bacteria and fungi can form deposits on metal surfaces, building slime layers and producing organic acids that cause pitting and accelerate corrosion of pipelines and associated metal structures. Replacing corrosion-damaged pipelines and related industrial infrastructure each year represents a serious drain on the nation's, and indeed the  
15 world's economic output.

Currently used methods of controlling biofouling fall generally into two categories: chemical and abrasive. Of these methods, chemical controls are generally considered to be the most effective, both in performance and cost. However, the efficacy of chemicals where  
20 biofilms are concerned is limited by the natural defense mechanisms of the embedded microorganisms. *Planktonic* or free-floating organisms are readily destroyed by many chemical agents used to control microorganisms. But *sessile*, or fixed organisms located on pipeline surfaces, are protected by a polysaccharide covering, or *glycocalyx*, and will have some success in warding off the effect of even fairly toxic biocides. An increased dose of toxin may or may  
25 not succeed in overcoming the protection provided by this polysaccharide covering, because these polymers restrict permeability of the biofilm by most biocides.

A wide variety of biocides that are capable of killing planktonic microorganisms are cited in the literature; see, for example, U. S. Patent No. 4,297,224. They include the oxidizing  
30 biocides: chlorine, bromine, chlorine dioxide, chloroisocyanurates and halogen-containing hydantoins. They also include the non-oxidizing biocides: quaternary ammonium compounds,

isothiazolones, aldehydes, parabens and organo-sulfur compounds. Traditionally, the above biocides have been employed to kill planktonic microorganisms in circulating water systems such as, for example, chemical refinery cooling systems or industrial pasteurizers. Until relatively recently, little routine monitoring of biocidal efficacy versus sessile microorganisms had been performed. Studies have confirmed that many widely used biocides are relatively ineffective against sessile microorganisms; see, for example, Costerton *et al.* (1988).

As noted above, abrasive methods of biofouling control can also be used. These methods include simple manual removal of slime, cleaning with high pressure water streams, use of cleaning "pigs" or other methods making use of a longitudinally inserted shaft, and sand blasting. To illustrate some of the disadvantages of abrasive cleaning, consider the following technique for cleaning the interior of pipes and tubing by a device that comprises a flexible longitudinal shaft with one end connected to a circular brush and the other end connected to a motor that rotates the shaft for turning the brush. The motor is generally electrically or air driven. The device is inserted within the tube or pipe to be cleaned, and herein lies the first problem: the tubes and pipes to be cleaned are limited in length to the shaft length. In this method, the maximum pipe length is limited by the friction of the trailing flex shaft/tube casing on the inside of the pipe. The minimum tubing diameter size is approximately 3/4 inch due to the required size of the flex shaft and case. Another problem is that the device is inoperable around bends of 90 degrees. Yet an additional problem is that the trailing flex-shaft and casing are very difficult to clean and maintain in a clean state under use. Also, this device is expensive to operate since it requires power such as electricity and/or shop air to run the motors in addition to, preferably, a pressurized water or cleaning solution. Other disadvantages of this and various other abrasive cleaning methods include (i) the need for protection of non-metallic surfaces such as expansion joints and valve seals, (ii) the extensive piping systems which are required for water jet cleaning, (iii) the labor-intensive nature of these methods, and (iv) the necessity of removing spent abrasive with methods such as sand blasting.

Clearly, a need exists for an effective, low toxicity method of removing and preventing water system biofouling which overcomes the disadvantages of currently known and implemented chemical and abrasive cleaning methods.

### SUMMARY OF THE INVENTION

The present invention provides novel compositions and methods for controlling or reducing biofouling of pipelines, and aqueous circulating or non-circulating systems. The compositions include one or more chelators in combination with one or more biocidal or antibiotic compounds to be used to contact an area or surface susceptible to biofouling, and in some embodiments to biofouling by microorganisms.

For the purposes of this disclosure, the phrase "a chelator" denotes one or more chelators. As used herein, the term "chelator" is defined as a molecule comprising nonmetal atoms, two or more of which atoms are capable of linking or binding with a metal ion to form a heterocyclic ring including the metal ion.

For the purposes of this disclosure, the phrase "an antifungal agent" denotes one or more antifungal agents. As used herein, the term "antifungal agent" is defined as a compound having either a fungicidal or fungistatic effect upon fungi contacted by the compound.

As used herein, the term "fungicidal" is defined to mean having a destructive killing action upon fungi. As used herein, the term "fungistatic" is defined to mean having an inhibiting action upon the growth of fungi.

For the purposes of this disclosure, the phrase "an antibacterial agent" denotes one or more antibacterial agents. As used herein, the term "antibacterial agent" is defined as a compound having either a bactericidal or bacteristatic effect upon bacteria contacted by the compound.

As used herein, the term "bactericidal" is defined to mean having a destructive killing action upon bacteria. As used herein, the term "bacteristatic" is defined to mean having an inhibiting action upon the growth of bacteria.

For the purposes of this disclosure, the phrase "an antimicrobial agent" denotes one or more antimicrobial agents. As used herein, the term "antimicrobial agent" is defined as a compound having either a microbicidal or microbistatic effect upon microbes or microorganisms contacted by the compound.

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As used herein, the term "microbicidal" is defined to mean having a destructive killing action upon microbes or microorganisms. As used herein, the term "microbistatic" is defined to mean having an inhibiting action upon the growth of microbes or microorganisms.

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As used herein the terms "microbe" or "microorganism" are defined as very minute, microscopic life forms or organisms, which may be either plant or animal, and which may include, but are not limited to, algae, bacteria, and fungi.

15

As used herein the terms "contact", "contacted", and "contacting", are used to describe the process by which an antimicrobial agent, e.g., any of the compositions disclosed in the present invention, comes in direct juxtaposition with the target microbe colony.

Preferable chelators for use in the present invention include, but are not limited to, ethylenediamine-N,N,N',N'-tetraacetic acid (EDTA); the disodium, trisodium, tetrasodium, dipotassium, tripotassium, dilithium and diammonium salts of EDTA; the barium, calcium, cobalt, copper, dysprosium, europium, iron, indium, lanthanum, magnesium, manganese, nickel, samarium, strontium, and zinc chelates of EDTA; trans-1,2-diaminocyclohexane-N,N,N',N'-tetraacetic acid monohydrate; N,N-bis(2-hydroxyethyl)glycine; 1,3-diamino-2-hydroxypropane-N,N,N',N'-tetraacetic acid; 1,3-diaminopropane-N,N,N',N'-tetraacetic acid; 25 ethylenediamine-N,N'-diacetic acid; ethylenediamine-N,N'-dipropionic acid dihydrochloride; ethylenediamine-N,N'-bis(methylenephosphonic acid) hemihydrate; N-(2-hydroxyethyl)ethylenediamine-N,N',N'-triacetic acid; ethylenediamine-N,N,N',N'-tetakis(methylenephosphonic acid); O,O'-bis(2-aminoethyl)ethyleneglycol-N,N,N',N'-tetraacetic acid; N,N-bis(2-hydroxybenzyl)ethylenediamine-N,N'-diacetic acid; 1,6- 30 hexamethylenediamine-N,N,N',N'-tetraacetic acid; N-(2-hydroxyethyl)iminodiacetic acid; iminodiacetic acid; 1,2-diaminopropane-N,N,N',N'-tetraacetic acid; nitrilotriacetic acid;

nitrilotripropionic acid; the trisodium salt of nitrilotris(methylenephosphoric acid); 7,19,30-trioxa-1,4,10,13,16,22,27,33-octaazabicyclo [11.11.11] pentatriacontane hexahydrobromide; and triethylenetetramine - N,N,N',N'',N''',N''''-hexaacetic acid.

5 More preferably, the chelators for use in conjunction with the present invention may include ethylenediamine-N,N,N',N'-tetraacetic acid (EDTA); the disodium, trisodium, tetrasodium, dipotassium, tripotassium, dilithium and diammonium salts of EDTA; 1,3-diamino-2-hydroxypropane-N,N,N',N'-tetraacetic acid; 1,3-diaminopropane-N,N,N',N'-tetraacetic acid; O,O'-bis(2-aminoethyl)ethyleneglycol-N,N,N',N'-tetraacetic acid; and 7,19,30-  
10 trioxa-1,4,10,13,16,22,27,33-octaazabicyclo [11.11.11] pentatriacontane hexahydrobromide.

Most preferably, the chelators for use in the present invention may include ethylenediamine-N,N,N',N'-tetraacetic acid (EDTA); the disodium salt of EDTA; 1,3-diaminopropane-N,N,N',N'-tetraacetic acid; and O,O'-bis(2-aminoethyl)ethyleneglycol-  
15 N,N,N',N'-tetraacetic acid.

The chelators of the present invention may be delivered to an aqueous system at a dosage ranging from about 0.1 parts per million (ppm) to about 10,000 ppm, more preferably at a dosage ranging from about 1.0 ppm to about 5000 ppm, and most preferably at a dosage  
20 ranging from about 50 ppm to about 2500 ppm, including all intermediate dosages therebetween. It will be readily understood that "intermediate dosages", in these contexts, means any dosages between the quoted ranges, such as about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, *etc.*; 3, 4, 5, 6, 7, 8, 9, 10, *etc.*; 12, 13, 14, *etc.*; 50, 51, 52, 53, 54, *etc.*; 100, 101, 102, 103, 104, *etc.*; 500, 501, 502, 503, *etc.*; 600, 700, 800, 900, 1000, *etc.*; 2000, 3000, 4000, 5000, 6000,  
25 7000, 8000, 9000, and about 10,000 ppm, and including all fractional dosages therebetween.

In another embodiment, it is contemplated that the chelators of the present invention may be delivered to an aqueous system at a dosage ranging from about 200 parts per million  
30 (ppm) to about 500 ppm, including all intermediate dosages therebetween. It will be readily understood that "intermediate dosages", in these contexts, means any dosages between the



quoted ranges, such as about 201, 202, 203, 204, *etc.*; 250, 251, 252, 253, *etc.*; 300, 301, 302, 303, 304, *etc.*; 350, 351, 352, 353, 354, *etc.*; 400, 401, 402, 403, 404, *etc.*; 450, 451, 452, 453, 454, *etc.*; 496, 497, 498, 499, and about 500 ppm and including all fractional dosages therebetween.

5

In still another embodiment, it is contemplated that the chelators of the present invention may be delivered to an aqueous system at a dosage ranging from about 500 parts per million (ppm) to about 1000 ppm, including all intermediate dosages therebetween. It will be readily understood that "intermediate dosages", in these contexts, means any dosages between the quoted ranges, such as about 501, 502, 503, 504, *etc.*; 550, 551, 552, 553, *etc.*; 600, 601, 602, 603, 604, *etc.*; 650, 651, 652, 653, 654, *etc.*; 700, 701, 702, 703, 704, *etc.*; 750, 751, 752, 753, 754, *etc.*; 801, 802, 803, 804, *etc.*; 850, 851, 852, 853, *etc.*; 900, 901, 902, 903, 904, *etc.*; 950, 951, 952, 953, 954, *etc.*; 996, 997, 998, 999 and about 1000 ppm and including all fractional dosages therebetween.

15

In yet another embodiment, it is contemplated that the chelators of the present invention may be delivered to an aqueous system at a dosage ranging from about 1000 parts per million (ppm) to about 5000 ppm, including all intermediate dosages therebetween. It will be readily understood that "intermediate dosages", in these contexts, means any dosages between the quoted ranges, such as about 1001, 1002, 1003, 1004, *etc.*; 1501, 1502, 1503, 1504, *etc.*; 2000, 2001, 2002, 2003, 2004, *etc.*; 2500, 2501, 2502, 2503, 2504, *etc.*; 3000, 3001, 3002, 3003, 3004, *etc.*; 3500, 3501, 3502, 3503, 3504, *etc.*; 4000, 4001, 4002, 4003, 4004, *etc.*; 4500, 4501, 4502, 4503, *etc.*; 4996, 4997, 4998, 4999 and about 5000 ppm and including all fractional dosages therebetween.

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By "about" is meant "approximately" or "in the vicinity of." For example, the phrase "about 100" may mean 101, 102, 103, 104, *etc.*, and fractional values therebetween, and it may also mean 95, 96, 97, 98, 99, *etc.*, and fractional values therebetween.

30

Many antifungal agents are known to those of skill in the art and may be useful in the present invention. For example, antifungal agents contemplated for use in the present invention include, but are not limited to, new third generation triazoles such as UK 109,496

(Voriconazole); SCH 56592; ER30346; UK 9746; UK 9751; T 8581; and Flutrimazole; cell wall active cyclic lipopeptides such as Cilofungin LY121019; LY303366 (Echinocandin); and L-743872 (Pneumocandin); allylamines such as Terbinafine; imidazoles such as Omoconazole, Ketoconazole, Terconazole, Econazole, Itraconazole and Fluconazole; polyenes such as

5 Amphotericin B, Nystatin, Natamycin, Liposomal Amphotericin B, and Liposomal Nystatin; and other antifungal agents including Griseofulvin; BF-796; MTCH 24; BTG-137586; RMP-7/ Amphotericin B; Pradimicins (MNS 18184); Benanomycin; Ambisome; ABLC; ABCD; Nikkomycin Z; and Flucytosine.

10 More preferably, the antifungal agents for use in conjunction with the present invention may include polyenes such as Amphotericin B, Nystatin, Natamycin, Liposomal Amphotericin B, and Liposomal Nystatin; cell wall active cyclic lipopeptides such as Cilofungin LY121019; LY303366 (Echinocandin); and L-743872 (Pneumocandin); and other antifungal agents including Griseofulvin and Flucytosine.

15

Most preferably, the antifungal agents for use in the present invention may include Amphotericin B, Nystatin, Liposomal Amphotericin B, and Liposomal Nystatin. Preferably, the antifungal/chelator composition is introduced in amounts sufficient to kill biofouling microorganisms at film forming surfaces of the system and thereafter to maintain the

20 concentration of the antifungal/chelator composition at a level sufficient to reduce substantially the regrowth of such microorganisms at such surfaces.

The antifungal agents of the present invention may be delivered to an aqueous system at a dosage ranging from about 0.01 parts per million (ppm) to about 1000 ppm, more preferably

25 at a dosage ranging from about 0.1 ppm to about 100 ppm, and most preferably at a dosage ranging from about 0.5 ppm to about 10 ppm, including all intermediate dosages therebetween. It will be readily understood that "intermediate dosages", in these contexts, means any dosages between the quoted ranges, such as about 0.01, 0.02, 0.03, *etc.*; 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9,

30 *etc.*; 3, 4, 5, 6, 7, 8, 9, 10, *etc.*; 12, 13, 14, *etc.*; 50, 51, 52, 53, 54, *etc.*; 100, 101, 102, 103, 104,

*etc.*; 150, 151, 152, 153, *etc.*; 500, 501, 502, 503, *etc.*; 600, 700, 800, 900, and about 1000 ppm, and including all fractional dosages therebetween.

In another embodiment, it is contemplated that the chelators of the present invention may be delivered to an aqueous system at a dosage ranging from about 200 parts per million (ppm) to about 500 ppm, including all intermediate dosages therebetween. It will be readily understood that "intermediate dosages", in these contexts, means any dosages between the quoted ranges, such as about 201, 202, 203, 204, *etc.*; 250, 251, 252, 253, *etc.*; 300, 301, 302, 303, 304, *etc.*; 350, 351, 352, 353, 354, *etc.*; 400, 401, 402, 403, 404, *etc.*; 450, 451, 452, 453, 454, *etc.*; 496, 497, 498, 499, and about 500 ppm and including all fractional dosages therebetween.

In still another embodiment, it is contemplated that the chelators of the present invention may be delivered to an aqueous system at a dosage ranging from about 500 parts per million (ppm) to about 1000 ppm, including all intermediate dosages therebetween. It will be readily understood that "intermediate dosages", in these contexts, means any dosages between the quoted ranges, such as about 501, 502, 503, 504, *etc.*; 550, 551, 552, 553, *etc.*; 600, 601, 602, 603, 604, *etc.*; 650, 651, 652, 653, 654, *etc.*; 700, 701, 702, 703, 704, *etc.*; 750, 751, 752, 753, 754, *etc.*; 801, 802, 803, 804, *etc.*; 850, 851, 852, 853, *etc.*; 900, 901, 902, 903, 904, *etc.*; 950, 951, 952, 953, 954, *etc.*; 996, 997, 998, 999 and about 1000 ppm and including all fractional dosages therebetween.

Because biofouling is caused by various organisms including algae, bacteria, protozoans, and the like, other types of antibiotics may also be added to the chelator/antifungal compositions described above. Such agents may include, but are not limited to aminoglycoside, ampicillin, carbenicillin, cefazolin, cephalosporin, chloramphenicol, clindamycin, erythromycin, everninomycin, gentamycin, kanamycin, lipopeptides, methicillin, nafcillin, novobiocin, oxazolidinones, penicillin, polymyxin, quinolones, rifampin, streptogramins, streptomycin, sulfamethoxazole, sulfonamide, tetracycline, trimethoprim and vancomycin.

The antibiotics of the present invention may be delivered to an aqueous system at a dosage ranging from about 0.01 parts per million (ppm) to about 1000 ppm, more preferably at a dosage ranging from about 0.1 ppm to about 100 ppm, and most preferably at a dosage ranging from about 0.5 ppm to about 10 ppm, including all intermediate dosages therebetween.

5 It will be readily understood that "intermediate dosages", in these contexts, means any dosages between the quoted ranges, such as about 0.01, 0.02, 0.03, *etc.*; 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, *etc.*; 3, 4, 5, 6, 7, 8, 9, 10, *etc.*; 12, 13, 14, *etc.*; 50, 51, 52, 53, 54, *etc.*; 100, 101, 102, 103, 104, *etc.*; 500, 501, 502, 503, *etc.*; 600, 700, 800, 900, and about 1000 ppm, and including all  
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In still another embodiment, it is contemplated that the chelators of the present invention may be delivered to an aqueous system at a dosage ranging from about 500 parts per million (ppm) to about 1000 ppm, including all intermediate dosages therebetween. It will be readily understood that "intermediate dosages", in these contexts, means any dosages between  
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Other active agents may include additional algicides, fungicides, corrosion inhibitors, scale inhibitors, complexing agents, surfactants, enzymes, nonoxidizing biocides and other compatible products which will lend greater functionality to the product. The other active agents of the present invention may be delivered to an aqueous system at a dosage known by those skilled in the art to be efficacious.

Other biocides that may be used are: ortho-phthalaldehyde, bromine, chlorine, ozone, chlorine dioxide, chlorhexidine, chloroisocyanurates, chlorine donors, formaldehyde, glutaraldehyde, halogen-containing hydantoins, a peroxy salt (a salt which produces hydrogen peroxide in water), a percarbonate, peracetate, persulfate, peroxide, or perborate salt, quaternary ammonium compounds, isothiazolones, parabens, silver sulfonamides, and organo-sulfur compounds. The other biocides of the present invention may be delivered to an aqueous system at a dosage known by those skilled in the art to be efficacious.

#### BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

**FIGS. 1 - 17** display plots of microbial population vs. time for cultures of species of *Aspergillus*, *Candida*, *Fusarium*, and certain bacteria. Response of these cultures to treatment with antimicrobials, chelators, and combinations thereof are indicated.

**FIG. 1** shows the inhibitory effect of EDTA on *Aspergillus flavus* *in vitro*.

**FIG. 2** shows the inhibitory effect of EDTA on *Aspergillus terreus* *in vitro*.

**FIG. 3** shows the inhibitory effect of EDTA on *Fusarium oxysporum* *in vitro*.

**FIG. 4** shows the inhibitory effect of EDTA on *Candida krusei* *in vitro*.

**FIG. 5** shows the synergistic inhibition of *Aspergillus fumigatus* by Amphotericin B and EDTA (1.0 mg/mL) *in vitro*.

**FIG. 6** shows the synergistic inhibition of *Aspergillus fumigatus* by Amphotericin B and EDTA (0.1 mg/mL) *in vitro*.

**FIG. 7** shows the synergistic inhibition of *Aspergillus flavus* by Amphotericin B and EDTA (1.0 mg/mL) *in vitro*.

**FIG. 8** shows the synergistic inhibition of *Aspergillus flavus* by Amphotericin B and EDTA (0.1 mg/mL) *in vitro*.

5 **FIG. 9** shows the synergistic inhibition of *Fusarium solani* by Amphotericin B and EDTA *in vitro*.

**FIG. 10** shows the synergistic inhibition of *Aspergillus fumigatus* by Ambisome and EDTA (0.1 mg/mL) *in vitro*.

10 **FIG. 11** shows the synergistic inhibition of *Fusarium solani* by Ambisome and EDTA *in vitro*.

**FIG. 12** shows the inhibitory effect of EDTA on vanomycin resistant enterococci *in vitro*.

**FIG. 13** shows the inhibitory effect of EDTA on multidrug resistant *S. maltophilia* *in vitro*.

15 **FIG. 14** shows the inhibitory effect of EDTA on multidrug resistant *Pseudomonas* *in vitro*.

**FIG. 15** shows the synergistic inhibition of vanomycin resistant enterococci by minocycline and EDTA *in vitro*.

20 **FIG. 16** shows the synergistic inhibition of *S. maltophilia* by gentamycin and EDTA *in vitro*.

**FIG. 17** shows the synergistic inhibition of *S. maltophilia* by polymyxin B and EDTA *in vitro*.

## DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

25 The present invention provides compositions and methods for the prevention and treatment of biofouling in water containing or submerged systems. The invention arises from the inventors' discovery that chelators have a significant growth inhibitory effect against species of fungal and bacterial microorganisms including *Aspergillus*, *Fusarium*, *Candida*, *Pseudomonas*, vancomycin-resistant enterococci, and multidrug resistant *Stenotrophomonas*  
30 (see data in **FIGS. 1 - 4, 12 - 14**). Also, the inventors have demonstrated that, when combined with antifungal agents, chelators show additive to synergistic inhibitory activity against the

growth of fungal microorganisms (see data in FIGS. 5 - 11). The inventors have further demonstrated that, when combined with antimicrobial compounds, chelators show additive to synergistic inhibitory activity against the growth of bacterial microorganisms (see data in FIGS. 15 - 17). These discoveries provide the basis for a novel program of prevention and treatment of microbial biofoulings using any of several embodiments of the inventive formulations, which may comprise various combinations of chelators, antifungal agents, antiseptic agents, antibacterial agents, and any necessary buffers, solvents, or surfactants.

All pipelines, including those which carry gas, oil, and water or other chemicals become contaminated with bacterial and fungal microorganisms. The same is true for commercial and industrial aqueous process and water handling systems. These microorganisms form biofilm on the surfaces of these pipelines and systems. This biofilm or slime comprises the glycocalyx of the microbial organisms contained therein. Most eukaryotic cells have a carbohydrate-rich zone about their periphery, and this peripheral zone or cell coat is made up of oligosaccharide side chains of glycolipids and integral membrane glycoproteins. Embedded in the biofilm environment, microorganisms such as bacteria and fungi benefit from a form of "extrinsic" resistance, thus rendering organisms which are ordinarily intrinsically and biologically sensitive to antimicrobials more resistant than they would otherwise be.

Colonies that include several kinds of bacteria and fungi can form deposits on metal surfaces, building slime layers and producing organic acids that cause pitting and accelerate corrosion of pipelines and associated metal structures. The inventors have shown that EDTA and other chelators of the present invention assist in disrupting and/or dissolving the glycocalyx of microbial colonies adherent to venous catheters. See, for example, United States Patent 5,362,754 by Raad *et al.*, or United States patent application S/N 08/317,309 by Raad *et al.*, both of which are herein incorporated by reference. The disruption and/or dissolution of microbial slime improves the activity of antimicrobial compounds against the bacteria, fungi, and other microbes embedded in the slime.

As used herein, and as standard in the art, a chelate is a type of coordination compound in which a central metal ion is attached by coordinate links to two or more nonmetal atoms in

the same molecule. Heterocyclic rings are thus formed during chelation, with the metal atom as part of the ring. The molecule comprising the nonmetal linking atoms is termed a chelator. Chelators are used in various chemical applications, for example as titrating agents or as metal ion scavengers. Chelators can be used to remove ions from participation in biological reactions. For example, the well-known chelator ethylenediamine-N,N,N',N'-tetraacetic acid (EDTA) acts as an anticoagulant because it is capable of scavenging calcium ions from the blood.

It is known that iron and other trace metals are essential in the life cycle of microorganisms such as bacteria and fungi. Without these trace metals, microbes are unable to grow and reproduce. Although iron is abundant in nature, its availability for microbial assimilation is limited owing to the insolubility of ferric ions at neutral or alkaline pH. As a consequence, many microorganisms have evolved their own specialized trace metal-scavenging molecules, called siderophores, which bind with trace metals and make them available for uptake by bacteria and/or fungi. The chelators of the present invention have their inhibitory effect upon bacteria and fungi in part by virtue of competing with the microbial siderophores for any available trace metal ions. As noted above, the inventors have shown that EDTA and other chelators of the present invention assist in disrupting and/or dissolving the glycocalyx.

The inventors have discovered that chelators as described herein have significant growth inhibitory effect against many species of air- and water-borne microorganisms, including *Aspergillus*, *Fusarium*, *Candida*, *Pseudomonas*, vancomycin-resistant enterococci, and multidrug resistant *Stenotrophomonas* (see data in FIGS. 1 - 4, 12 - 14). This is a significant discovery because, as noted in the Background section, cooling water systems used in power-generating plants, refineries, chemical plants, air conditioning systems and other commercial and industrial operations frequently encounter biofilm problems due to contamination from airborne organisms entrained by air/water contact in cooling towers, as well as waterborne organisms from the systems' makeup water supply.

Referring to FIG. 1, it will be seen that EDTA exerts an inhibitory effect upon *Aspergillus flavus* relative to the control population. This effect is most clearly noticeable



beginning 12 h after application of the chelator. Referring to FIGS. 2 and 3, similar inhibitory behavior was noticed in cultures of *Aspergillus terreus* and multidrug resistant *Fusarium oxysporum* following application of EDTA. The inhibitory effect of EDTA on *Candida krusei* is noticeable only a few hours after contact of the fungus with the chelator, as shown in FIG. 4.

- 5 As seen in FIG. 12, EDTA has a pronounced inhibitory effect upon multidrug resistant enterococcus. Referring to FIGS. 13 and 14, it will be seen that EDTA exerts an inhibitory effect upon multidrug resistant *Stenotrophomonas maltophilia* and likewise upon multidrug resistant *Pseudomonas*, relative to the control populations; in both cases, this inhibitory effect is most clearly noticeable beginning approximately 4 h after application of the chelator.
- 10 Experimental conditions for the inhibition studies described in FIGS. 1 - 4 and 12 - 14 may be found under Example 1 below.

- Table 1 provides a representative list of chelators useful in conjunction with the present invention. Preferred chelators are those which bind trace metal ions with a binding constant ranging from about  $10^1$  to about  $10^{100}$ ; more preferred chelators are those which bind trace metal ions with a binding constant ranging from about  $10^{10}$  to about  $10^{80}$ ; most preferred chelators are those which bind trace metal ions with a binding constant ranging from about  $10^{15}$  to about  $10^{60}$ .

20

Table 1  
CHELATORS

ABBREVIATION	FULL NAME
EDTA free acid	Ethylenediamine-N,N,N',N'-tetraacetic acid
EDTA 2Na	Ethylenediamine-N,N,N',N'-tetraacetic acid, disodium salt, dihydrate
EDTA 3Na	Ethylenediamine-N,N,N',N'-tetraacetic acid, trisodium salt, trihydrate
EDTA 4Na	Ethylenediamine-N,N,N',N'-tetraacetic acid, tetrasodium salt, tetrahydrate
EDTA 2K	Ethylenediamine-N,N,N',N'-tetraacetic acid, dipotassium salt, dihydrate

Table 1 - Continued

ABBREVIATION	FULL NAME
EDTA 2Li	Ethylenediamine-N,N,N',N'-tetraacetic acid, dilithium salt, monohydrate
EDTA 2NH <sub>4</sub>	Ethylenediamine-N,N,N',N'-tetraacetic acid, diammonium salt
EDTA 3K	Ethylenediamine-N,N,N',N'-tetraacetic acid, tripotassium salt, dihydrate
Ba(II)-EDTA	Ethylenediamine-N,N,N',N'-tetraacetic acid, barium chelate
Ca(II)-EDTA	Ethylenediamine-N,N,N',N'-tetraacetic acid, calcium chelate
Ce(III) -EDTA	Ethylenediamine-N,N,N',N'-tetraacetic acid, cerium chelate
Co(II) -EDTA	Ethylenediamine-N,N,N',N'-tetraacetic acid, cobalt chelate
Cu(II) -EDTA	Ethylenediamine-N,N,N',N'-tetraacetic acid, copper chelate
Dy(III) -EDTA	Ethylenediamine-N,N,N',N'-tetraacetic acid, dysprosium chelate
Eu(III) -EDTA	Ethylenediamine-N,N,N',N'-tetraacetic acid, europium chelate
Fe(III) -EDTA	Ethylenediamine-N,N,N',N'-tetraacetic acid, iron chelate
In(III) -EDTA	Ethylenediamine-N,N,N',N'-tetraacetic acid, indium chelate
La(III) -EDTA	Ethylenediamine-N,N,N',N'-tetraacetic acid, lanthanum chelate
Mg(II) -EDTA	Ethylenediamine-N,N,N',N'-tetraacetic acid, magnesium chelate
Mn(II) -EDTA	Ethylenediamine-N,N,N',N'-tetraacetic acid, manganese chelate
Ni(II) -EDTA	Ethylenediamine-N,N,N',N'-tetraacetic acid, nickel chelate
Sm(III) -EDTA	Ethylenediamine-N,N,N',N'-tetraacetic acid, samarium chelate
Sr(II) -EDTA	Ethylenediamine-N,N,N',N'-tetraacetic acid, strontium chelate
Zn(II) -EDTA	Ethylenediamine-N,N,N',N'-tetraacetic acid, zinc chelate
CyDTA	trans-1,2-Diaminocyclohexane-N,N,N',N'-tetraacetic acid, monohydrate
DHEG	N,N-Bis(2-hydroxyethyl)glycine
DTPA-OH	1,3-Diamino-2-hydroxypropane-N,N,N',N'-tetraacetic acid
DTPA	1,3-Diaminopropane-N,N,N',N'-tetraacetic acid
EDDA	Ethylenediamine-N,N'-diacetic acid
EDDP	Ethylenediamine-N,N'-dipropionic acid dihydrochloride

Table 1 - Continued

ABBREVIATION	FULL NAME
EDDPO	Ethylenediamine-N,N'-bis(methylenephosphonic acid), hemihydrate
EDTA-OH	N-(2-Hydroxyethyl)ethylenediamine-N,N',N'-triacetic acid
EDTPO	Ethylenediamine-N,N,N',N'-tetrakis(methylenephosphonic acid)
EGTA	O,O'-bis(2-aminoethyl)ethyleneglycol-N,N,N',N'-tetraacetic acid
HBED	N,N-bis(2-hydroxybenzyl)ethylenediamine-N,N-diacetic acid
HDTA	1,6-Hexamethylenediamine-N,N,N',N'-tetraacetic acid
HIDA	N-(2-Hydroxyethyl)iminodiacetic acid
IDA	Iminodiacetic acid
Methyl-EDTA	1,2-Diaminopropane-N,N,N',N'-tetraacetic acid
NTA	Nitrilotriacetic acid
NTP	Nitrilotripropionic acid
NTPO	Nitrilotris(methylenephosphonic acid), trisodium salt
O-Bistren	7,19,30-Trioxa-1,4,10,13,16,22,27,33-octaazabicyclo [11,11,11] pentatriacontane, hexahydrobromide
TTHA	Triethylenetetramine - N,N,N',N'',N''',N''''-hexaacetic acid

The classes of compounds known currently to act as antifungal agents, and which are contemplated to be useful in the practice of the present invention include, but are not limited to, the polyenes, the imidazoles and triazoles, griseofulvin, and flucytosine. The polyenes bind to ergosterols in fungal membranes, resulting in the formation of transmembrane channels which allow the escape of metabolites essential to maintaining the viability of the fungal cell. The imidazoles and triazoles are structurally related and share the same antifungal spectrum and mechanism of action, namely the inhibition of the fungal sterol 14- $\alpha$ -demethylase enzyme system. Griseofulvin was isolated from a species of *Penicillium* and acts by inhibiting fungal mitosis. Flucytosine is a fluorinated pyrimidine which acts upon fungi by inhibiting thymidylate synthetase.

The inventors have demonstrated that Amphotericin B acts synergistically in concert with the chelator EDTA to inhibit many species of air- and water-borne microorganisms,

including *Aspergillus*, *Fusarium*, vancomycin-resistant enterococci, and multidrug resistant *Stenotrophomonas* (a drug combination is said to exhibit synergism when the combination achieves a desired effect one order of magnitude or greater than the analogous effect of the most potent individual constituent of the combination) See data in FIGS. 5 - 11, 15 - 17. This is significant because, as noted in the Background section, cooling water systems used in power-generating plants, refineries, chemical plants, air conditioning systems and other commercial and industrial operations frequently encounter biofilm problems due to contamination from airborne organisms entrained by air/water contact in cooling towers, as well as waterborne organisms from the systems' makeup water supply.

10

Referring to FIG. 5. Amphotericin B at a concentration of 1 µg/mL and EDTA at a concentration of 1 mg/mL act synergistically to inhibit the growth of *Aspergillus fumigatus* by a margin of almost two orders of magnitude relative to EDTA acting alone. The same effect is observed when the concentration of EDTA is reduced to 0.1 mg/mL (FIG. 6). Likewise, Amphotericin B and EDTA inhibit *Aspergillus flavus* synergistically, whether EDTA is present at 1.0 mg/mL or 0.1 mg/mL (FIGS. 7 and 8). This synergy extends to inhibition of *Fusarium solani* as well, as seen in FIG. 9. In FIGS. 10 and 11 the inhibitory effect of liposomal Amphotericin B and EDTA against *A. fumigatus* and *F. solani*, respectively, is demonstrated. In FIG. 15, the inhibitory effect of minocycline and EDTA against vancomycin-resistant enterococci is shown. FIG. 16 shows the synergistic inhibition of *S. maltophilia* by gentamycin and EDTA, and FIG. 17 shows the synergistic inhibition of *S. maltophilia* by polymyxin B and EDTA. Experimental conditions for the synergy studies described in FIGS. 5 - 11 and 15 - 17 may be found under Examples 2, 3 and 4 below.

Antifungal agents particularly preferred in connection with the present invention include the polyenes, most preferably Amphotericin B and all soluble forms of Amphotericin B, i.e. liposomal complexes, suspensions, and the like. Table 2 provides a representative list of antifungal agents useful in conjunction with the present invention. The list in Table 2 is not meant to be exhaustive.

25

Table 2

## ANTIFUNGALS

UK 109,496 (Voriconazole)	Terbinafine
SCH 56592	BF-796
ER30346	MTCH 24
UK 9746	BTG-137586
UK 9751	RMP-7/ Amphotericin B
T 8581	Omoconazole
Flutrimazole	Amphotericin B
Cilofungin LY121019	Nystatin
LY303366 (Echinocandin)	Natamycin
L-743872 (Pneumocandin)	Clotrimazole
Pradimicins (MNS 18184)	Miconazole
Benanomicin	Ketoconazole
Ambisome	Terconazole
ABLC	Econazole
Liposomal Amphotericin	Itraconazole
ABCD	Fluconazole
Liposomal Nystatin	Griseofulvin
Nikkomycin Z	Flucytosine

In addition, the present invention may be used in conjunction with or may alternate with known biofouling treatments. Such treatments may include, but are not limited to, non-oxidizing biocides such as isothiazolones, formaldehyde and glutaraldehyde. Other concurrent treatments may include the addition of acidic or alkaline compounds to control the pH level, or addition of oxidizing biocides to the water, such as chlorine, chlorine dioxide, chlorine donors, and ozone. Other sanitizing agents and systems which are known in the art may also be used with the methods and compositions of the present invention. For example, 0.1 - 1.0 parts per million (ppm) of copper and/or silver ions, 2 - 12 ppm alkyl, dialkyl, or polymeric quaternary ammonium compounds, or 6 - 10 ppm poly(hexamethylene biguanide), commonly referred to

as PHMB are all treatments standard in the art which may be used in conjunction with the practice of the present invention.

In U. S. Patent No. 5,449,658, Unhoch *et al.* describe the addition of a "potentiating  
5 adjuvant," ethylenediamine tetraacetic acid (EDTA), to PHMB in amounts sufficient to render  
the antimicrobial composition algicidal and fungicidal in water, followed by the use of a peroxy  
salt as a "backup agent" to discourage regrowth of microorganisms in the aqueous system being  
treated. Unhoch *et al.* recognized that at its usual dosages of 6 - 10 ppm, PHMB is bactericidal,  
but generally only algistatic and fungistatic. To improve the killing levels of PHMB against  
10 algae and fungi, the chelator EDTA is introduced at a dosage of 1.5 - 36 ppm, thus improving  
the efficacy of PHMB. However, Unhoch *et al.* failed to recognize that chelators can, by  
themselves, have an inhibitory effect against certain airborne and waterborne microorganisms.  
This is evidenced by their statement that "EDTA has been used as a chelating agent in  
swimming pools and spas to chelate metals such as iron to prevent staining or scale formation  
15 ... EDTA has no fungicidal or algicidal activity of its own ... and has not been used as an  
algistat or fungistat in swimming pools, spas, or the like." By contrast, the chelators of the  
present invention have been demonstrated to have a distinct inhibitory effect, acting either  
alone or in concert with antimicrobial agents, upon several well-known species of bacteria and  
fungi. Further, Unhoch *et al.* have not shown, as have the present inventors, that chelators such  
20 as those of the present invention may combine with antimicrobial agents such as those of the  
present invention to produce a synergistic inhibitory effect upon a wide spectrum of the slime-  
producing microorganisms which cause biofouling in commercial and industrial water systems.

The methods disclosed herein may be further enhanced by treating the water with a  
25 backup agent comprising a peroxy salt (a salt which produces hydrogen peroxide in water),  
such as a percarbonate, peracetate, persulfate, peroxide, or perborate, but preferably with an  
alkali metal perborate, in a manner similar to that described in U. S. Patent No. 4,253,971,  
which is incorporated herein by reference. For example, after an initial treatment of the water  
with a chelator/antimicrobial composition according to the present invention, the water may be  
30 further treated by adding a sodium perborate salt to the water at the rate of about 1 to 36 ppm  
per week, preferably about 12 to 24 ppm per week as a backup. Additionally, the method and

apparatus for ozonolysis of aqueous systems disclosed in U. S. Patent No. 5,591,349, incorporated herein by reference, may be used in conjunction with the compositions and methods of the present invention. For example, the method of treatment of the present invention could be alternated with the ozonolysis method to ensure effective, broad-spectrum  
5 killing of slime-producing microorganisms.

With benefit of the present disclosure, one of skill in the art will recognize that the compositions and methods of the present invention may be used in conjunction with any of the abrasive cleaning technologies known in the art. For example, U. S. Patent No. 5,615,696  
10 discloses a rotating, cleaning nozzle(s) which emits high pressure water or other fluids for cleaning the surfaces of a pipeline. The pressure of the water is established to effectively remove the coating or other material on the pipeline without damaging the substrate or pipe. Thus, the speed of the longitudinal movement of the cleaning apparatus along the pipeline, together with the rotational or linear speed of the rotating water jet, must also be determined in  
15 order to provide the most effective cleaning action without damage to the pipe. Thus, rotary seals associated with the rotating nozzles or swivel heads are subjected to vibrations and wear from the high pressures and speeds involved which results in a short life thereby requiring costly replacements. One of the key features of the disclosed apparatus is provision of a nozzle capable of sweeping over a broad area using a system operating at pressure over 30,000 pounds  
20 per square inch (psi). This system covers a wide area with a nozzle moving over the area. Nozzle movement, even rotating movement is accomplished by a piped system which does not have any high pressure seals in it. The nozzle movement is accommodated by a flexible hose connection to a moving nozzle with no seals to fail. One of skill in the art will recognize that the compositions of the present invention are ideal for use with such a rotating cleaning nozzle.

25 Similarly, the compositions of the present invention may be used with the water-driven turbine/brush assembly disclosed in U. S. Patent No. 5,406,666, incorporated herein by reference. A first embodiment includes an assembly comprising a small turbine with angled blades axially mounted between inner and outer rings, on one end of a standoff support. An O-ring for stabilizing the assembly within the pipe is mounted in a groove within the outer ring.  
30 A replaceable circular brush is fixedly mounted on the opposite end of the standoff support and

can be used for cleaning robes and pipes of various diameters, lengths and configurations. The turbine, standoff support, and brash spin in unison relative to a hub bearing that is fixedly attached to a wire upstream of the assembly. The nonrotating wire is for retaining the assembly in tension and enabling return of the assembly to the pipe entrance. The assembly is initially placed in the pipe or tube to be cleaned. A pressurized water or solution source is provided at a required flow-rate to propel the assembly through the pipe or tube. The upstream water pressure propels and spins the turbine, standoff support and brush. The rotating brush combined with the solution cleans the inside of the pipe. The solution flows out of the other end of the pipe with the brush rotation controlled by the flow-ram. One of skill in the art will recognize that the compositions of the present invention are ideal for use with such a water-driven turbine/brush assembly, such as by including the compositions of the present invention in the solutions of pressurized water used to drive the disclosed device.

Likewise, the spherical cleaning means comprising an annular gap which emits a conical jet of high-pressure liquid for cleaning a pipeline surface, disclosed in U. S. Patent No. 5,296,038, incorporated herein by reference, is suitable for use with the compositions of the present invention. This cleaning device is characterized in that the cleaning means is brought into contact with an inner wall of the line, such that a reduced pressure is established between the cleaning means and the inner wall and the cleaning means is made to move around about the cross-section of the line by twisting the supply conduit about its longitudinal axis. This reduced pressure is preferably established by bringing the annular gap on the cleaning means into close contact with the inner wall of the line and especially by adjusting the cleaning means to assume an angle against the inner wall of the line. The cleaning arrangement is further characterized in that the cleaning means has largely the shape of a ball wherein the continuous gap extends along the outermost periphery of the cleaning means, and a continuous gap is established by the back piece exhibiting an external conical surface extending along its periphery at its forward end, while the front piece presents a conical internal surface corresponding to the back piece of the conical surface in order to, when used, establish an annular gap, with the annular gap being directed back out towards the coupling means at an angle of up to 30-60 degrees.



The sandblasting method of U. S. Patent No. 5,239,786, incorporated herein by reference, the rotating brush method of U. S. Patent No. 5,235,718, incorporated herein by reference, the liquid flush/pig launch method of U. S. Patent No. 4,716,611, incorporated herein by reference, and the pressurized acid method of U. S. Patent No. 5,045,352, incorporated  
5 herein by reference, are all suitable for use in conjunction with the compositions and methods of the present invention.

Furthermore, although it may not qualify strictly as an abrasive cleaning method, the technique for cleaning a cooling tower disclosed in U. S. Patent No. 4,808,319, incorporated  
10 herein by reference, wherein multiple liquid phases flow through the packing material of the tower in a direction counter to the flow of an air phase, is suitable for use in connection with the compositions and methods of the present invention.

The following examples are included to demonstrate preferred embodiments of the  
15 invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still  
20 obtain a like or similar result without departing from the spirit and scope of the invention.

## EXAMPLE 1

### Inhibition Study

The following example demonstrates the inhibitory effect of chelators on species of  
25 *Aspergillus*, *Fusarium*, *Candida*, *Pseudomonas*, vancomycin-resistant enterococci, and multidrug resistant *Stenotrophomonas*. The data collected are displayed in FIGS. 1 - 4 and 12 - 14. A spectrophotometer was used at a frequency of 660 nanometers (nm) to measure the absorbency of the solution. For molds, all inocula were started at  $1 \times 10^4$  conidia/mL. For yeast and bacteria, all inocula were started at  $1 \times 10^6$  cfu/mL. The medium used was Mueller-  
30 Hinton.

The data in FIG. 1 demonstrate an inhibitory effect of EDTA on growth of *Aspergillus flavus* after a 12 h incubation. FIG. 2 shows a similar effect of EDTA on growth of *Aspergillus terreus*. EDTA is also shown to have a growth inhibitory effect on *Fusarium oxysporum* after 12 h (FIG. 3) and an inhibitory effect on *Candida krusei* that is apparent after only a four hour incubation period (FIG. 4). In addition, EDTA is shown herein to be an effective growth inhibitor of multidrug resistant enterococcus (FIG. 12), multidrug resistant *S. maltophilia* (FIG. 13), and multidrug resistant *Pseudomonas* (FIG. 14).

## EXAMPLE 2

### Synergy Study

The following example demonstrates the fungicidal effect of the combination of an antifungal and a chelator. In particular, the studies described herein are directed to determining the presence of a synergistic or additive effect for EDTA and Amphotericin B acting in concert, and for EDTA and Ambisome acting in concert. The studies were conducted in a laboratory incubator at a constant temperature of 30°C. The medium was a single lot of liquid RPMI 1640 medium (Whittaker Bioproducts, Inc., Walkersville, Md.) supplemented with 0.3 g of L-glutamine per liter and 0.165 M MOPS buffer (34.54 g/liter) and without sodium bicarbonate.

Test inocula contained approximately  $1 \times 10^3$  to  $1 \times 10^4$  conidia/mL. To induce conidium and sporangioophore formation, fungi were grown on sabouraud dextrose agar plates at 35°C for 5 to 7 days. Each fungus was then covered with approximately 2 mL sterile 0.85% saline water. The suspension was then harvested by gently probing the colonies with sterile glass rods. The resulting mixture of conidia or sporangioophores and hyphal fragments was withdrawn and filtered through a sterile 4 x 4 gauze to a sterile tube. The homogenous suspension was later mixed with a vortex mixer for 30 s and the densities of the suspension were read and adjusted to a range of 80 to 85% transmittance. Inoculum of 0.1 mL was delivered to each flask containing 20 mL of RPMI and drug dilution series. The final conidia concentration ranged from  $1 \times 10^3$  to  $1 \times 10^4$  conidia/mL. A control flask was maintained without any drugs. The flasks were incubated in a shaker at 30°C for 24 to 48 h. Glass beads were added to all flasks with visible fungal growth in an attempt to homogenize the solution

and achieve even distribution of conidia for culture. Cultures were done at 0, 4, 24, and 48 h on sabouraud dextrose agar plates and incubated at 35°C for 48 h.

Amphotericin B for injection, USP (Gensia Laboratories, Ltd.) was suspended and diluted in sterile water and stored at 1 mg/mL in a glass vial in the dark at -70°C. Ambisome was obtained in 50 mg vials and used immediately upon opening of the vial. Typically, 50 mg of Ambisome was diluted in 12 mL of sterile water. Further dilutions were performed as needed. Edetate disodium INJ., USP (Abbott Laboratories, North Chicago, IL) was stored at a concentration of 150 mg/mL at 4°C. Further dilutions were made to achieve the desired concentration of each drug at the time of the study. For Amphotericin B and Ambisome, the concentration was 1.0 µg/mL and for EDTA the concentrations were 0.1 and 1.0 mg/mL.

The data demonstrate the synergistic inhibitory effect of Amphotericin B and EDTA against *A. fumigatus* (FIG. 5 and FIG. 6), against *A. flavus* (FIG. 7 and FIG. 8) and against *Fusarium solani* (FIG. 9). The synergistic effect of a commercially available Amphotericin B formulation, Ambisome, and EDTA against *A. fumigatus* is shown in FIG. 10, and against *Fusarium solani* is shown in FIG. 11.

### EXAMPLE 3

#### Synergy Study

The following example demonstrates a synergistic effect of EDTA and gentamycin or EDTA and polymyxin B against the water-borne microbe *Stenotrophomonas maltophilia*. The study was conducted in 15 mL Falcon brand tubes. Seven tubes were filled with 5 mL each of Mueller-Hinton broth; one tube contained EDTA, one tube contained gentamycin, one tube contained polymyxin B, one tube contained EDTA + gentamycin, one tube contained EDTA + polymyxin B, and one tube contained no chelators or antimicrobial agents (as a control). The concentration for each of the active compounds remained constant at 8 µg/mL for gentamycin, 1 mg/mL for EDTA, and 0.5 µg/mL for polymyxin B.

The synergistic effects are shown in FIG. 16 for EDTA + gentamycin and FIG. 17 for polymyxin B + EDTA.

## EXAMPLE 4

### Preparation of Minocycline + EDTA

The present example provides a detailed description of how the minocycline + EDTA preparation is prepared. The minocycline + EDTA solution is prepared as follows so as to achieve a concentration of about 3 mg/mL minocycline and about 30 mg/mL EDTA in a saline solution. Separate solutions of EDTA (60 mg/mL) and minocycline (3 mg/mL) are prepared in saline. The EDTA is reconstituted from 200 mg/mL Edetate Calcium Disodium (Versen<sup>®</sup>, 3M Riker, Northridge, CA) or reconstituted from Edetate Disodium [150 mg/mL parenteral concentrate (Endrate<sup>®</sup>, Abbott, Chicago, IL, or Disolate<sup>®</sup>, Forest, Maryland Heights, MO)]. Alternatively, the 60 mg/mL of EDTA can be reconstituted from EDTA powder (Sigma Chemical Co., St. Louis, MO). Minocycline is obtained from Lederle and combined with a volume of saline sufficient to constitute about 3 mg/mL minocycline. The 6 mg/mL minocycline and 60 mg/mL EDTA solutions are mixed in equal volumes to constitute a 3 mg minocycline and 30 mg EDTA/mL solution.

Once formulated, the minocycline + EDTA may be stored refrigerated at 4°C until use. It is contemplated that so formulated, the solution will remain chemically stable and active for at least 1 month at 4°C. The preparation is also very stable at room temperature (37°C) for at least 72 h.

The synergistic effects for EDTA + minocycline against vancomycin-resistant enterococci are shown in FIG. 15.

## EXAMPLE 5

### Chelating Agent Combinations With Antimicrobial Agents

The present example provides a representative list of specific combinations of ingredients expected for use in the practice of the present invention as a flushing solution. The term antimicrobial agent as used in the description of the present invention includes non-glycopeptide antibiotics and antifungal agents. A representative list of these antimicrobial agents, particularly defined as non-glycopeptide antimicrobial agents, is provided in the general

textbook reference of Sanford (1994), which reference is specifically incorporated herein by reference for this purpose.

A representative list of antibiotics, chelators and complexing agents that may be used in the preparation of the various embodiments of the invention includes:

**Antibiotics**

aminoglycoside  
ampicillin  
10 carbenicillin  
cefazolin  
cephalosporin  
chloramphenicol  
clindamycin  
15 erythromycin  
everninomycin  
gentamycin  
kanamycin  
lipopeptides  
20 methicillin  
nafcillin  
novobiocin  
oxazolidinones  
penicillin  
25 polymyxin  
quinolones  
rifampin  
streptogramins  
streptomycin  
30 sulfamethoxazole  
sulfonamide  
tetracycline

**Antibiotics - Continued**

trimethoprim  
vancomycin

5   **Chelators**

deferoxamine  
dimercaprol  
DMSA  
penicillamine  
10   succimer

**Complexing Agents**

ammonium-1-pyrrolidine dithiocarbamate  
bathophenanthroline

15

**Antiseptic Agents**

chlorhexidine  
silver sulfonamide  
chlorine  
20   bromine

**Specific combinations contemplated by the inventors include:**

EDTA + minocycline

EDTA + minocycline rifampin

25   EGTA + non-glycopeptide antibiotics (*e. g.* tetracycline antibiotic + minocycline,  
doxycycline, oxytetracycline)

Triethylene tetraminedihydrochloride (TTH) + tetracycline antibiotic (minocycline,  
doxycycline, oxytetracycline)

Hirudin + tetracycline antibiotic (minocycline, doxycycline, oxytetracycline)

30   Diethylene triamine pentaacetic acid (DTPA) + tetracycline antibiotic (minocycline,  
doxycycline, oxytetracycline)

Diethylenetriamineacetic acid + tetracycline antibiotic (minocycline, doxycycline, oxytetracycline)

Triethylene tetramine dihydrochloride + tetracycline antibiotic (minocycline, doxycycline, oxytetracycline)

5 Etidronate® (disodium dihydrogen (1-hydroxyethylidene) bis[phosphonate]) + tetracycline antibiotic (minocycline, doxycycline, oxytetracycline)

Dimercaprol + tetracycline antibiotic (minocycline, doxycycline, oxytetracycline).

Citrate + tetracycline antibiotic (minocycline, doxycycline, oxytetracycline).

10 Methanamine + tetracycline antibiotic (minocycline, doxycycline, oxytetracycline).

EDTA is available as calcium sodium EDTA and sodium EDTA formulations. The most preferred form employed by the present inventors is sodium EDTA. These formulations are provided at a concentration of 150 mg/mL.

15 As will be appreciated by those of skill in the art, the present list is only intended to be exemplary. Other chelating agents are also expected to be useful in combination with a non-glycopeptide antibiotic or other antimicrobial substance with equal efficacy. In addition, rifampin or any of the rifamycin family of antibiotics, may also be used in the practice of the present invention. These combinations formulated as a coating will preferably further include a  
20 material that will enhance adherence or film forming characteristics, of the preparation.

REFERENCES

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

- 5           Costerton *et al.*, "Bacterial Biofilms in Relation to Internal Corrosion Monitoring and Biocide Strategies", In: *Materials Performance*, p.49, 1988.
- Sanford, *et al.*, In: *Guide to Antimicrobial Therapy*, pp. 118, Table 28, 1994.
- United States Patent No. 4,253,971
- United States Patent No. 4,297,224
- 10           United States Patent No. 4,716,611
- United States Patent No. 4,808,319
- United States Patent No. 5,045,352
- United States Patent No. 5,235,718
- United States Patent No. 5,239,786
- 15           United States Patent No. 5,296,038
- United States Patent No. 5,362,754
- United States Patent No. 5,406,666
- United States Patent No. 5,449,658
- United States Patent No. 5,591,349
- 20           United States Patent No. 5,615,696
- United States Patent Application S/N 08/317,309



CLAIMS

1. A method for controlling growth, in an aqueous system, of microorganisms which adhere to walls and other structural surfaces of the system, which method comprises providing to said aqueous system a composition comprising a chelating agent and an antimicrobial compound in an amount at least effective to control said growth.
2. The method of any one of claims 1, 10, 11, 12 or 13 wherein said chelating agent is selected from the group consisting of Ethylenediamine-N,N,N',N'-tetraacetic acid, Ethylenediamine-N,N,N',N'-tetraacetic acid, disodium salt, dihydrate, Ethylenediamine-N,N,N',N'-tetraacetic acid, trisodium salt, trihydrate, Ethylenediamine-N,N,N',N'-tetraacetic acid, tetrasodium salt, tetrahydrate, Ethylenefismir-N,N,N',N'-tetraacetic acid, dipotassium salt, dihydrate, Ethylenediamine-N,N,N',N'-tetraacetic acid, dilithium salt, monhydrate, Ethylenediamine-N,N,N',N'-tetraacetic acid, diammonium salt, Ethylenediamine-N,N,N',N'-tetraacetic acid, tripotassium salt, dihydrate, Ethylenediamine-N,N,N',N'-tetraacetic acid, barium chelate, Ethylenediamine-N,N,N',N'-tetraacetic acid, calcium chelate, Ethylenediamine-N,N,N',N'-tetraacetic acid, cerium chelate, Ethylenediamine-N,N,N',N'-tetraacetic acid, cobalt chelate, Ethylenediamine-N,N,N',N'-tetraacetic acid, copper chelate, Ethylenediamine-N,N,N',N'-tetraacetic acid, dysprosium chelate, Ethylenediamine-N,N,N',N'-tetraacetic acid, europium chelate, Ethylenediamine-N,N,N',N'-tetraacetic acid, iron chelate, Ethylenediamine-N,N,N',N'-tetraacetic acid, indium chelate, Ethylenediamine-N,N,N',N'-tetraacetic acid, lanthanum chelate, Ethylenediamine-N,N,N',N'-tetraacetic acid, magnesium chelate, Ethylenediamine-N,N,N',N'-tetraacetic acid, manganese chelate, Ethylenediamine-N,N,N',N'-tetraacetic acid, nickel chelate, Ethylenediamine-N,N,N',N'-tetraacetic acid, samarium chelate, Ethylenediamine-N,N,N',N'-tetraacetic acid, strontium chelate, Ethylenediamine-N,N,N',N'-tetraacetic acid, zinc chelate, trans-1,2-Diaminocyclohexane N,N,N',N'-tetraacetic acid, monohydrate, N,N-Bis(2-hydroxyethyl)glycine, 1,3-Diamino-2-hydroxypropane-N,N,N',N'-tetraacetic acid, 1,3-Diaminopropane-N,N,N',N'-tetraacetic acid, Ethylenediamine-N,N'-diacetic acid, Ethylenediamine-N,N'-dipropionic acid dihydrochloride, Ethylenediamine-N,N'-bis(methylenephosphonic acid), hemihydrate,

- N-(2-Hydroxyethyl)ethylenediamine-N,N',N'-triacetic acid, Ethylenediamine-N,N,N',N'-tetraakis(methylenephosphonic acid), O,O'-bis(2-aminoethyl)ethyleneglycol-N,N,N',N'-tetraacetic acid, N,N-bis(2-hydroxybenzyl)ethylenediamine-N,N-diacetic acid, 1,6-Hexamethylenediamine-N,N,N',N'-tetraacetic acid, N-(2-Hydroxyethyl)iminodiacetic acid, Iminodiacetic acid, 1,2-Diaminopropane-N,N,N',N'-tetraacetic acid, Nitrilotriacetic acid, Nitrilotripropionic acid, Nitrilotris(methylenephosphoric acid), trisodium salt, 7,19,30-Trioxa-1,4,10,13,16,22,27,33-octaazabicyclo [11,11,11] pentatriacontane, hexahydrobromide and Triethylenetetramine - N,N,N',N'',N''',N''''-hexaacetic acid.
- 5
- 10 3. The method of any one of claims 1, 10, 11, 12 or 13 wherein said chelating agent is Ethylenediamine-N,N,N',N'-tetraacetic acid.
4. The method of any one of claims 1, 10, 11, 12 or 13 wherein said antifungal agent is selected from the group consisting of UK 109,496 (Voriconazole), Terbinafine, SCH 15 56592, BF-796, ER30346, MTCH 24, UK 9746, BTG-137586, UK 9751, RMP-7/ Amphotericin B, T 8581, Omoconazole, Flutrimazole, Amphotericin B, Cilofungin LY121019, Nystatin, LY303366 (Echinocandin), Natamycin, L-743872 (Pneumocandin), Clotrimazole, Pradimicins (MNS 18184), Miconazole, Benanomycin, Ketoconazole, Ambisome, Terconazole, ABLC, Econazole, Liposomal Amphotericin, 20 Itraconazole, ABCD, Fluconazole, Liposomal Nystatin, Griseofulvin, Nikkomycin Z, and Flucytosine.
5. The method of any one of claims 1, 10, 11, 12 or 13 wherein a sufficient amount of said composition is maintained in the aqueous system to inhibit the regrowth of said fungi.
- 25 6. The method of any one of claims 1, 10, 11, 12 or 13 wherein said composition further comprises an antialgal, antibacterial or antiseptic compound.
7. The method of any one of claims 1, 10, 11, 12 or 13 wherein said composition further 30 comprises ortho-phthalaldehyde, glutaraldehyde, or formaldehyde.

8. The method of any one of claims 1, 10, 11, 12 or 13 wherein the aqueous system is a recirculating cooling tower, an oil field water flood system, an air washer, or an air conditioning system.
- 5 9. The method of any one of claims 1, 10, 11, 12 or 13 wherein the aqueous system is used in the manufacture of paper, as a metal working fluid, a heat transfer fluid, a radiator fluid, a cooling system fluid, a conveyor lubricant, an oilfield drilling fluid, or a wastewater processing fluid.
- 10 10. A method for controlling, in an aqueous system, the biofouling of the walls and other structural surfaces of the system by a microorganism, said method comprising providing to said system a composition comprising a chelating agent and an antimicrobial agent in an amount at least sufficient to control said biofouling.
- 15 11. A method for removing or reducing formation of a biofilm in an aqueous system, comprising providing to said system a composition comprising a chelating agent and an antimicrobial agent in an amount at least sufficient to remove or reduce formation of said biofilm.
- 20 12. A method for inhibiting the growth of a microorganism, comprising contacting said microorganism with a composition comprising a chelating agent and an antimicrobial agent in an amount at least sufficient to inhibit the growth of said fungus.
13. A method for controlling the growth of microorganisms on the interior surface of a pipe,  
25 comprising contacting said surface with a microbicidally-effective amount of a composition comprising an antimicrobial agent and a chelator.
14. A method for inhibiting the growth of a bacterium, comprising contacting said bacterium with a composition comprising a chelating agent and an antibiotic in an  
30 amount at least sufficient to inhibit the growth of said bacterium.

15. A method for controlling the growth of bacteria on the interior surface of a pipe, comprising contacting said surface with a bactericidally-effective amount of a composition comprising an antibiotic and a chelator.
- 5 16. A method for inhibiting the growth of a fungus, comprising contacting said fungus with a composition comprising a chelating agent and an antifungal agent in an amount at least sufficient to inhibit the growth of said fungus.
- 10 17. A method for controlling the growth of fungi on the interior surface of a pipe, comprising contacting said surface with a fungicidally-effective amount of a composition comprising an antifungal agent and a chelator.
- 15 18. A method for removing or reducing formation of a biofilm in an aqueous system, comprising providing to said system a composition comprising a chelating agent and an antimicrobial agent *via* moving, rotating, high speed water jet nozzles.
19. A method for removing or reducing formation of a biofilm in an aqueous system, comprising providing to said system a composition comprising a chelating agent and an antimicrobial agent *via* a water driven turbine brush cleaning device.
- 20 20. A method for removing or reducing formation of a biofilm in an aqueous system, comprising providing to said system a composition comprising a chelating agent and an antimicrobial agent *via* a spherical cleaning device comprising an annular gap which emits a conical jet of pressurized fluid.

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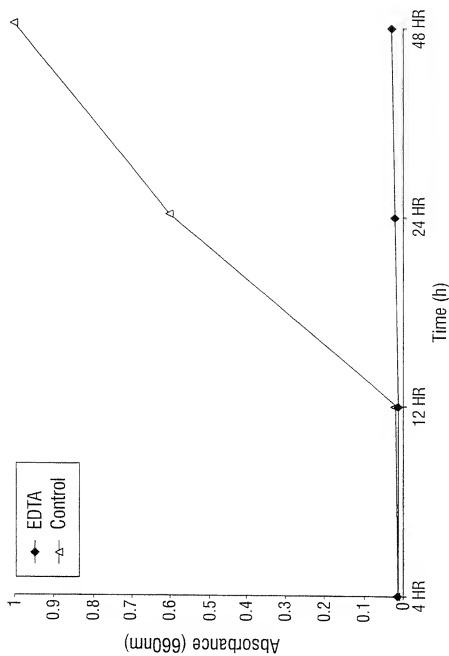


FIG. 1

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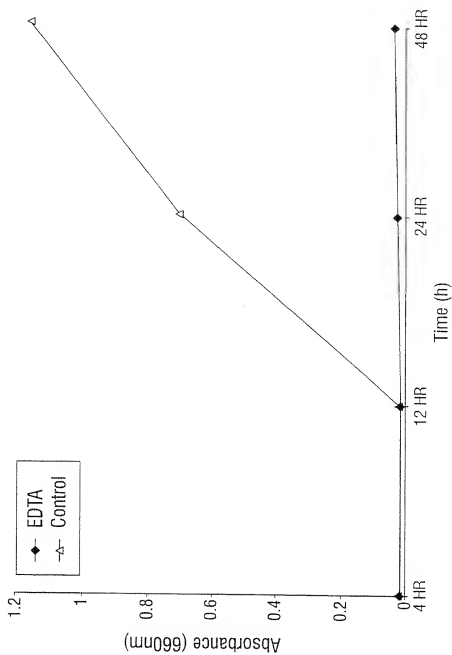


FIG. 2

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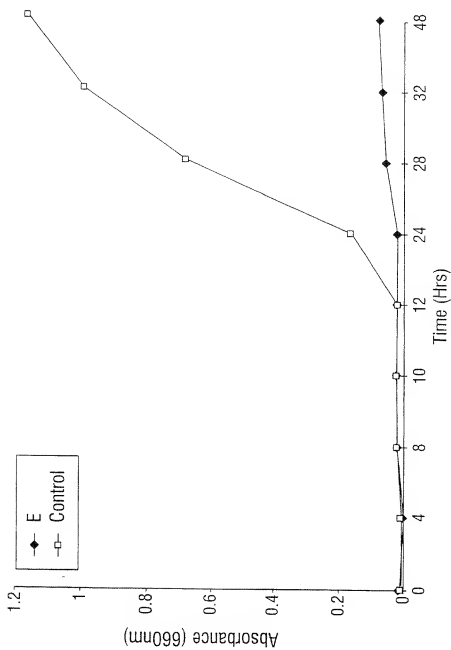


FIG. 3

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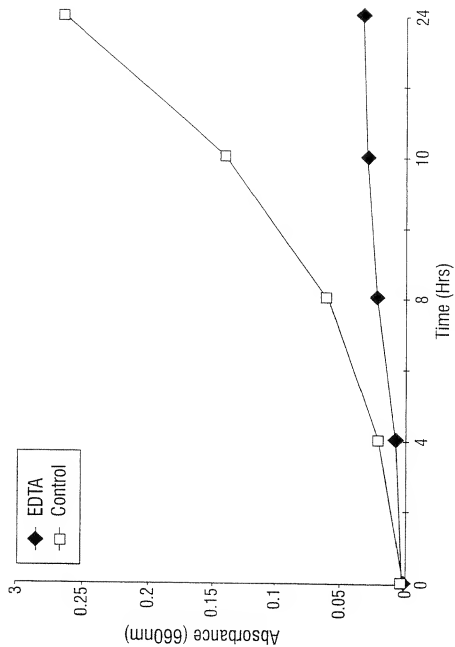


FIG. 4



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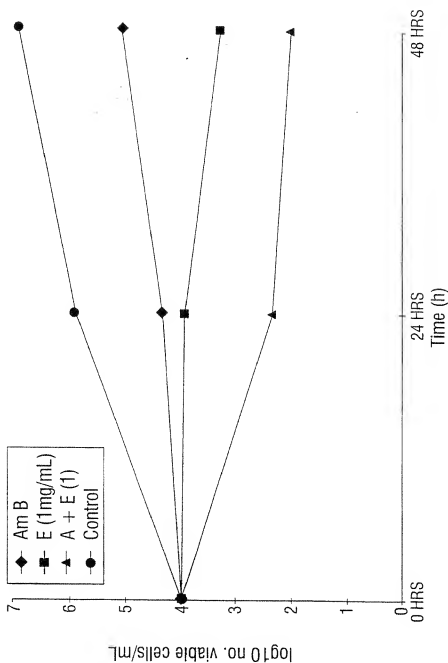


FIG. 5

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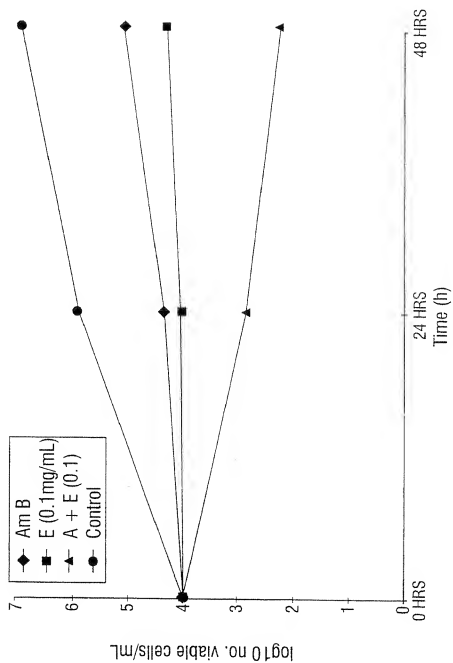


FIG. 6

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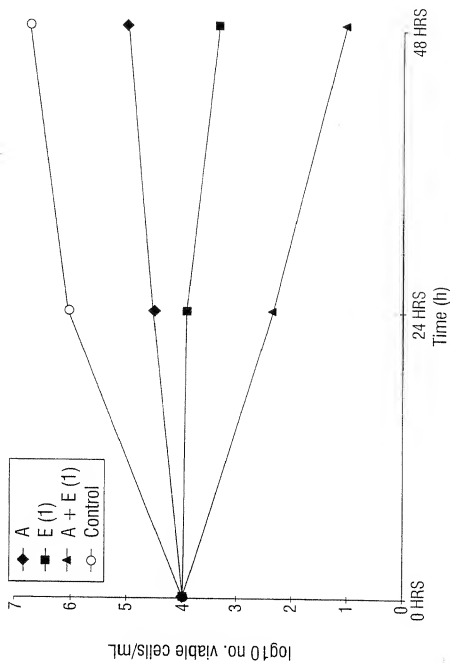


FIG. 7

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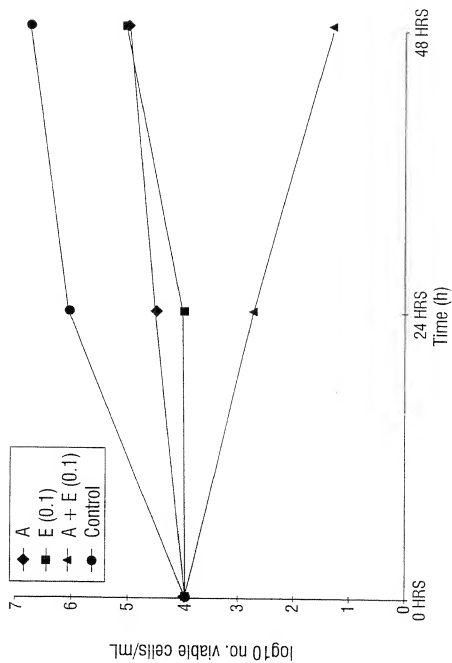


FIG. 8

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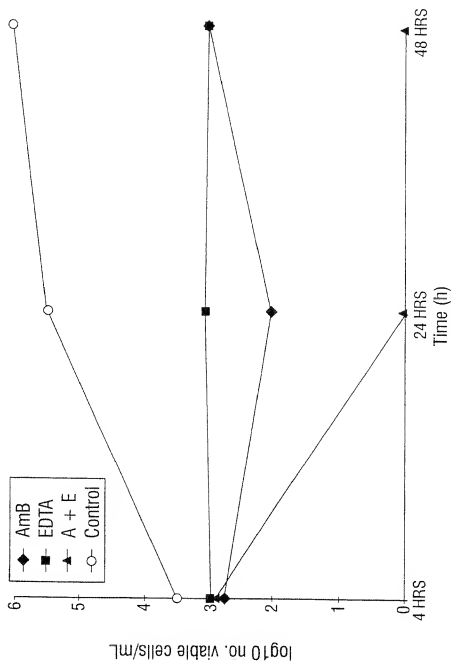


FIG. 9

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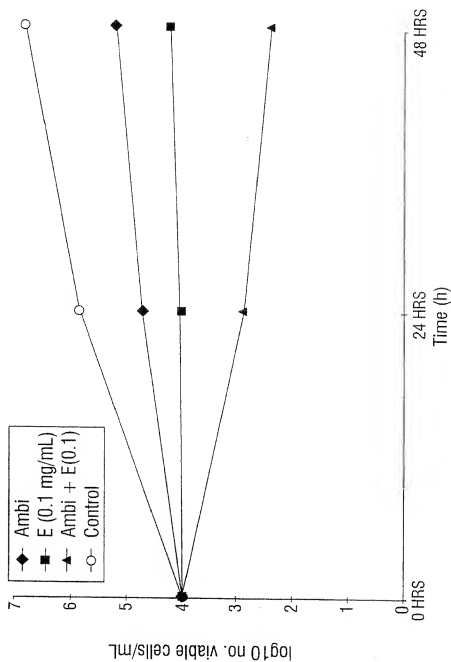


FIG. 10

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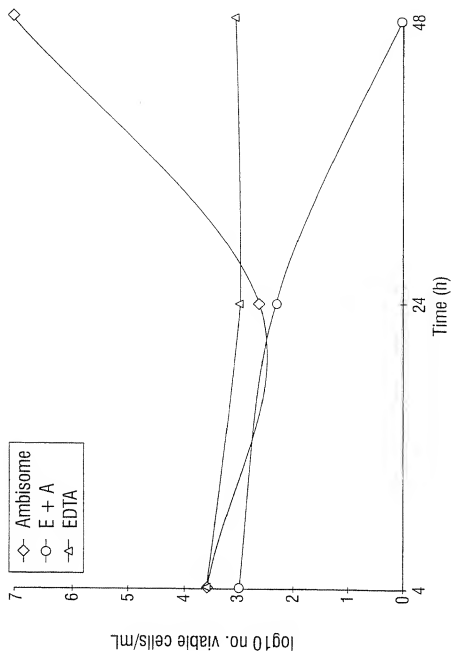


FIG. 11

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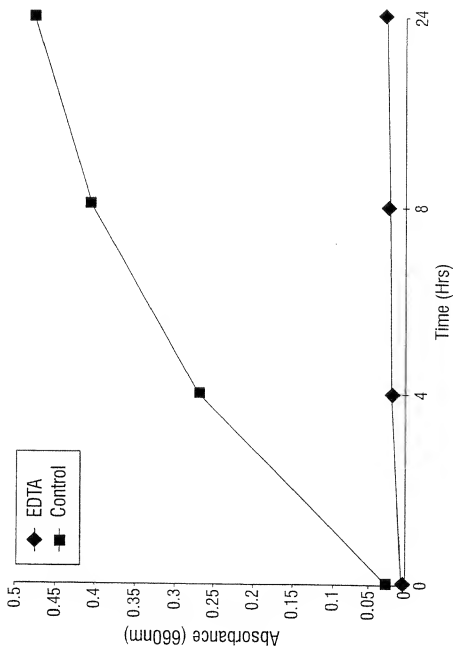


FIG. 12



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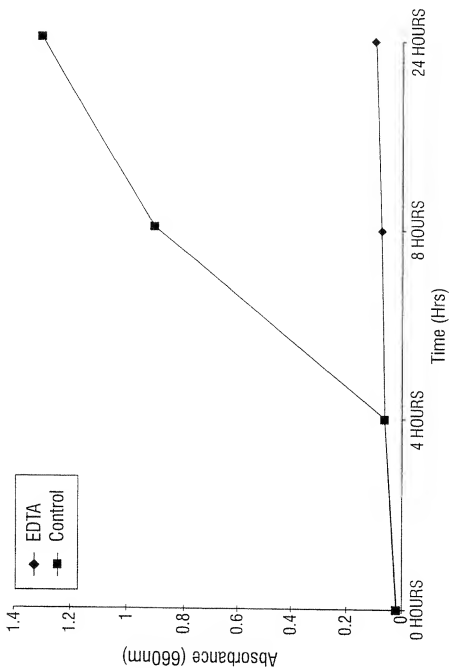


FIG. 13

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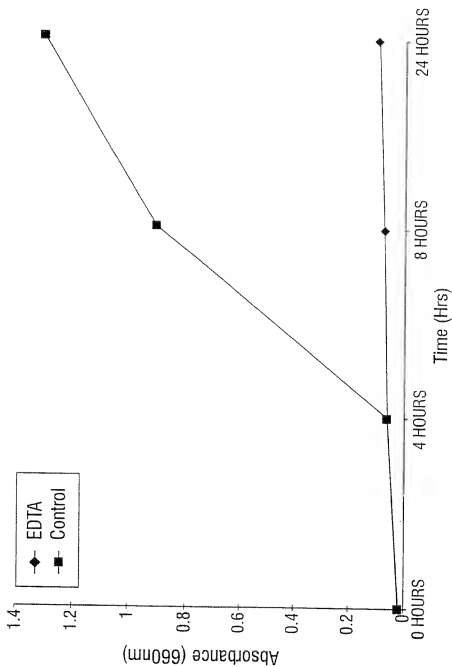


FIG. 14

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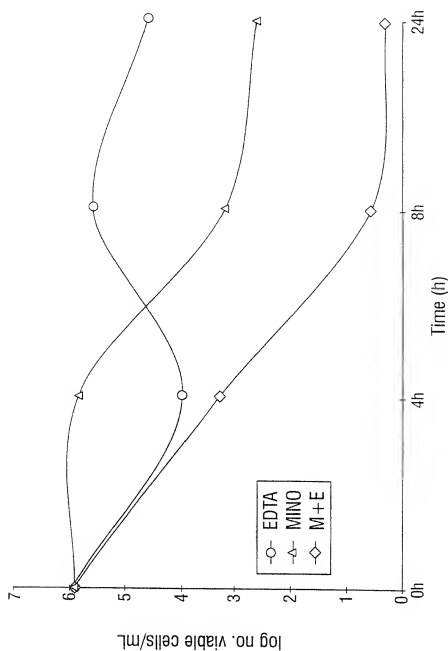


FIG. 15

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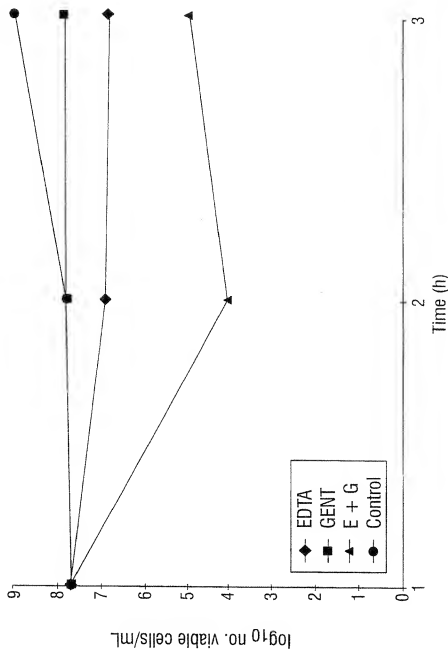


FIG. 16

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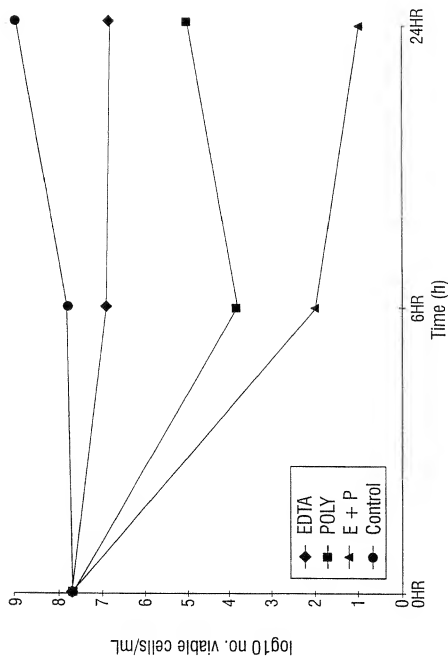


FIG. 17

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/17563

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : 134/22.14, 22.19, 23, 24; 210/749, 764; 510/199, 383, 386, 434.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 134/22.11-22.15, 23, 24; 210/749, 764; 510/199, 382-391, 434.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
APS, CAS ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,449,658 A (UNHOCH et al.) 12 September 1995, see col. 2, lines 10-14; claims 1-8 in cols. 9-10.	1-3, 5, 6, 8-17 ----- 18-20
X --- Y	WO 96/20737 A (UNIVERSITE DE MONTREAL) 11 July 1996, see p. 1, lines 6-29; p. 4, lines 3-28; p. 5, lines 5-20; p. 6, lines 22-26; p. 7, lines 6-14; p. 11, lines 14-20.	1-3, 5, 6, 8-17 ----- 18-20
Y	US 5,615,696 A (LAWLER) 01 April 1997, see entire document in general.	18
Y	US 5,406,666 A (WERLINK) 18 April 1995, see entire document in general.	19
Y	US 5,296,038 A (FAXON) 22 March 1994, see entire document in general.	20

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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*P* document published prior to the international filing date but later than the priority date claimed	*A*	document member of the same patent family

Date of the actual completion of the international search 09 NOVEMBER 1998	Date of mailing of the international search report <b>30 DEC 1998</b>
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer <i>Ardrith Hertzog</i> ARDITH HERTZOG Telephone No. (703) 308-0661

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/17563

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,784,790 A (DISCH et al.) 15 November 1988, see claims in cols. 7-8, especially claim 1, part (c), & claim 13.	1-3, 5-7, 10-17
X	US 5,395,541 A (CARPENTER et al.) 07 March 1995, see abstract; col. 19, line 49 - col. 20, line 12; col. 23, lines 59, especially; lines 52-53; col. 24, lines 55-65; col. 25, lines 3-15, especially lines 14-15, & lines 39-41, especially line 41; col. 25, line 52 - col. 26, line 8; col. 28, lines 2-6.	1-4

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/17563

A. CLASSIFICATION OF SUBJECT MATTER:  
IPC (6):

A61L 2/16, 2/18; B08B 3/08, 9/02, 9/04; C02F 1/50, 1/68; C11D 3/33, 3/48; C12S 9/00.





## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 7/48, 7/32, 7/11</b>		<b>A1</b>	(11) International Publication Number: <b>WO 99/38484</b>
			(43) International Publication Date: 5 August 1999 (05.08.99)
(21) International Application Number: PCT/IB99/00120		(81) Designated States: AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 25 January 1999 (25.01.99)			
(30) Priority Data: 9802044.9 31 January 1998 (31.01.98) GB			
(71) Applicant (for all designated States except US): THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US).			
(72) Inventors; and			
(75) Inventors/Applicants (for US only): SIMPSON, Anthony, Joseph [GB/GB]; 17 Sheringham Drive, Cramlington, Northumberland NE23 8HB (GB). HEINZMAN, Stephen, Wayne [US/GB]; Deleval Old Vicarage, Seaton Sluice, Whitley Bay NE26 4QW (GB). JANSEN, Judith, Ester [NL/GB]; 27 Shaftesbury Grove, Heaton, Newcastle upon Tyne NE6 5FA (GB).			
(74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217-1087 (US).			
Published With international search report.			
(54) Title: ANTI-ENZYME COMPOSITIONS COMPRISING ETHYLENEDIAMINE DISUCCINIC ACID			
(57) Abstract			
<p>The invention relates to composition for reduction of the enzyme activity of enzymes in contact with the human or animal body, in particular of enzymes present in the exudates, and to the use of specific complexing agents, including ethylene diamine disuccinic acid or a salt (EDDS), for preparation of these compositions.</p>			

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## ANTI-ENZYME COMPOSITIONS COMPRISING ETHYLENEDIAMINE DISUCCINIC ACID

The invention relates to compositions, which can be administered or applied to a human or animal, to inhibit or reduce the enzyme activity.

Background

Various types of enzymes are present in the our body or on our skin, including enzymes from bacteria's, enzymes derived from our diet and enzymes produced by the body.

It is know that some of these enzymes can have undesirable side-effects. For example, lipase enzymes are present in the body exudates and these enzymes are known to cause dermatitis or skin rash, which for example, has always been a problem encountered by the users of disposable absorbent articles, such as diapers, incontinence artieles, sanitary towels, training pants etc.

Manufacturers of diapers and skin care products have developed various products over the past decades which help reduce the occurrence of diaper rash (or skin rash). The main focus thereby has been to reduce the exposure of the skin to the body exudates. This is for example done by introduction to the diaper of absorbing or better absorbing materials. The amount of water which is in contact with the skin is thus reduced.

Lipase enzymes are also responsible for the production of fatty acids, which are partially eliminated from the body in the body exudates. These fatty acids can cause a malodour of the body.

EP 0117632-B relates to disposable articles which comprise lipase inhibiting agents, preferably zinc containing components, and a vehicle material. US 3,091,241 relates to the use of triacetine in vaginal tampons to inhibit lipase enzyme activity. US 3, 961,486 teaches the use of adipic acid to reduce the lipase enzyme activity and to reduce the skin rash.

It is known that the activity of various enzymes, such as lipase enzymes, is depended on the presence of certain metal ion, such as iron and copper, a so-called metallic cofactor. It has been

suggested to use EDTA complexing agents to react with the metallic cofactors, to reduce the enzyme activity (for example in NL 7506962).

However, it has been found that EDTA is not an effective complexing agents for the metal ions of the metallic cofactors, in particular when other metal ions are present on the skin or in the compositions.

The inventors now found that certain complexing agents, in particular ethylene diamine disuccinic acid (EDDS), can very effectively inactivate or inhibit the enzymes, by interacting with the metallic cofactor, containing metal ions such as copper and iron, and particularly when other ions, such as calcium ions, are present. Since calcium ion concentrations are generally high in body exudates or on the surface of the skin or hair, the complexing agents of the invention will be more effective when administered to humans or animals or applied to their skin or hair, than known complexing agents such as EDTA.

Thus, for example, it has been found that the use of the complexing agents in compositions of the invention, results in a very effective reduction or a prevention of dermatitis or malodour of the body, also when calcium ions are present in the compositions or on the skin, and for example, it has been found that even very small amounts of these complexing agents in these compositions can effectively give the required prevention or reduction of dermatitis or malodour of the body.

#### Summary of the Invention

The invention provides a composition comprising ethylene diamine disuccinic acid or a salt (EDDS) for reduction of the enzyme activity, preferably of enzymes in contact with the human or animal body, in particular of enzymes present in the exudates.

The invention also provides compositions for reduction of the enzyme activity, preferably of enzymes in contact with the human or animal body, comprising a complexing agent, and in use additionally comprising calcium ions and one or more metal ions, selected from the group

consisting of Cu, Fe, Zn, Ni, Co (herein referred to as 'the selected metal ions'), whereby the  $-\log_{10}C_T$  is equal to or greater than the smallest value of A or B, where

$$A \text{ is } -\log_{10}(L_T - M_T) \text{ and } B \text{ is } K_1(1 - K_2 \sqrt{I})(1 - K_3 \exp(-K_4 P)),$$

$C_T$  is the total concentration of calcium ions,  $L_T$  is the total concentration of complexing agent,  $M_T$  is the total concentration of the metal ions, selected from the group consisting of Cu, Fe, Zn, Ni and Co;  $P$  is the pH of the composition,  $I$  is the ionic strength of the composition, wherein all concentrations are in moles/litre, where  $K_1$ ,  $K_2$ ,  $K_3$  and  $K_4$  are the following constants for the metals ions:

	Cu <sup>++</sup>	Fe <sup>+++</sup>	Zn <sup>++</sup>	Ni <sup>++</sup>	Co <sup>++</sup>
K1	11.062	5.754	7.963	13.098	7.642
K2	0.496	0.479	0.619	0.535	0.652
K3	2.479	9385.0	24.202	1.473	32.069
K4	0.227	1.092	0.506	0.126	0.532

The invention also provides the use of the complexing agents as defined above, including ethylene diamine disuccinic acid or a salt (EDDS) for preparation of a composition for reduction of the enzyme activity, preferably of enzymes in contact with the human or animal body, in particular of enzymes present in the exudates.

#### Detailed Description of the Invention

The compositions of the invention reduce the enzyme activity of various enzymes, which require a metallic cofactor, in particular cofactors containing iron, copper, cobalt, zinc or nickel metal ions, by inhibiting or inactivating the enzymes.

The enzymes can be from bacteria's, fungi or algae, or can be produced by the human or animal body, or can be derived from the diet.

In particular esterase enzymes, including lipase enzymes, are very effectively inhibited or inactivated by the compositions of the invention.

The compositions can be used in any application where reduction of the enzyme activity of these enzymes is required. In particular, the compositions are used for reduction of the enzyme activity of enzymes in contact with the human or animal body, in particular the skin.

According to a preferred aspect of the invention, in use a source of calcium ions is also present in the composition. Hereby is meant that the calcium ions can be present in the composition containing the EDDS prior to use or in use, the calcium ion can be introduced in the

compositions, e.g. by the application of the compositions to the skin, which contains calcium ions.

In a highly preferred aspect of the invention, the compositions are used for reduction of the enzyme activity of enzymes present in the exudates, in particular esterase enzymes, including lipase enzymes.

The compositions are particularly useful when calcium ions are present in the compositions and/ or in contact with the human or animal body.

In preferred embodiments of the invention, the compositions comprising the complexing agents are useful for the treatment of enzymatic dermatitis or the treatment of formation of a malodour of the body, caused by enzymes, in particular for reduction of the enzyme activity of lipase enzymes.

The compositions may be cosmetic compositions, preferably in the form of a spray, cream, foam, lotion, gel, oil, ointment or powder or tablet, preferably in the form of a water-in-oil emulsion.

Highly preferred are compositions are comprised in a deoderant or absorbent articles, such as diapers, wet wipes, as described herein.

By treatment is meant herein an improvement of the affected condition of the human or animal body, caused by the enzyme activity. Thus includes in one preferred aspect of the invention, the reduction or at least stabilisation of the malodour of the body, which is caused by enzymes; in another preferred aspect of the invention, the reduction or at least stabilisation of the enzymatic dermatitis or the rash of the skin, caused by enzymes.

The amount of the composition of the invention used for the reduction of the enzyme activity or in the treatment, will vary with the particular location of the condition being treated, the severity of the condition being treated, the expected duration of the treatment, any specific sensitivity to either the composition specific to the user, the condition of the user, concurrent therapies being administered, other conditions present in the user.

For the present invention it is preferred that a minimum inhibitory concentration of the compositions containing the complexing agent is, preferably topically, applied to act as a complexing agent for selected metal ions present on the skin, which are required by the enzymes for their enzymatic performance, in an amount and form such that it is available to inhibit the activity of the enzymes present, particularly in the presence of calcium ions.

The complexing agents or compositions are in particular useful for the reduction of the enzyme activity of esterase enzymes, and thus for inhibition or inactivation of esterases, such as lipases or lipolytic enzymes. Their general activity is to hydrolyse fats present in the ester form (such as the glycerides found in human skin), and accordingly generate fatty acids and glycerol, which can cause irritation and malodour of the body. Because this group of enzymes is so widely distributed in plants, moulds, bacteria, milk, and milk-products, as well as in almost all animal tissues, and because moreover human lipase enzymes are present in the pancreatic exudates, they are almost always present in or on the human or animal body.

The activity of these lipases contributes to almost all skin rash or in particular diaper rash, causing irritation by the digestive degenerative action of lipase on the skin per se and by breaking down the lipid skin-components compromises the barrier property of the skin in the affected area. This breakdown of the integrity of the skin allows other components of the body exudates (urine and faeces in particular), which may not, by themselves, be irritating, to migrate through the compromised skin. At this point normally harmless components may then become irritating.

Highly preferred additional components of the compositions of the invention may be bactericidal or fungicidal agents, and/ or other enzyme inhibitors. Highly preferred can be the inclusion of cationic organic compounds, such as cationic surfactants.

#### pH Measurement

The pH as used herein can be determined by any known method of calculating or measuring the pH of an aqueous solution.



### Ionic Strength Measurement

The ionic strength (I) can be determined by the following equation:

$$I = \frac{1}{2} \sum c_i z_i^2,$$

wherein c is the molecular concentration of the soluble ion (i) and z is the charge of the soluble ion (i).

### Complexing Agent

A highly preferred complexing agent for use in compositions of the invention is N, N'- ethylene diamine disuccinic acid or its salt (EDDS).

It is known that the (S,S) EDDS isomer is more readily biodegradable than the (R,R) isomer. Thus, depending of the application of the aqueous compositions of the invention, it may be desirable to use only one of the isomers of EDDS. It may be preferred that a racemic mixture of the isomers is used in the aqueous compositions, for example because the racemic mixture is less expensive.

The exact level of incorporation of the complexing agents in the compositions of the invention will depend on the nature of the compositions and the mode of applications. However, in general even small amounts of complexing agents can be sufficient to obtain the required prevention or reduction of dermatitis. Typical amount of complexing agents can be from 0.001% by weight to 30% by weight, more preferably from 0.005% to 10%, more preferably from 001% to 5% by weight of the composition..

### Method of Preparation of the Compositions

The compositions can be prepared by any method known in the art for preparation for cosmetic compositions or medicament. The exact method will depend on the nature of the composition. The complexing agent can be added to the compositions in its acid or salt form, or be combined

with other ingredients commonly used in cosmetic compositions or medicaments, or dispersed or dissolved in water or oil or a water-in-oil emulsion prior to addition to the composition.

#### Method of Use of Compositions

The composition of the invention can be administered to the patient or user by any method known in the art, but preferably the composition is applied to the skin or hair, which will be in contact with, or the vicinity of the enzymes.

The compositions can also be applied (firstly) to an article, such as a wipe or tissue, which will then be applied to the skin.

When the composition is used for treatment of malodour of the body, the composition may preferably be in the form of a deodorant composition, in the form of a fluid, gel, cream or powder, contained in a stick or spray.

#### Absorbent Articles

The compositions of the present invention can be comprised in an absorbent article, preferably a disposable absorbent article. Particularly preferred absorbent articles therefor is a wipe or a diaper. The diaper preferably comprises the composition in the topsheet of the diaper.

As used herein, the term "absorbent articles" refers to devices which absorb and contain body exudates, and, more specifically, refers to devices which are placed against or in proximity to the body of the wearer to absorb and contain the various exudates discharged from the body. The term "disposable" is used herein to describe absorbent articles which are not intended to be laundered or otherwise restored or reused as an absorbent article (i.e., they are intended to be discarded after a single use and, preferably, to be recycled, composted or otherwise disposed of in an environmentally compatible manner).

The structure of the disposable absorbent article is not critical to the practice of the present invention.

Normally, the composition is incorporated into the absorbent article or diaper in particular in an amount which will deliver the required treatment or reduction or inhibition of the enzyme activity, whereby it may be preferred that this is achieved after frequent use.

The disposable absorbent article preferably contains the composition according to the invention at a level such that the complexing agents therein are present at a level of from 0.01% to 30%, more preferably from 0.01% to 10%, most preferably from 0.05% to 5% by weight of the article.

#### Additional Ingredients

The composition of the invention can comprise additional ingredients. Which ingredients are present and at which level depends on the character of the composition and the use thereof. Thus for example lotions will generally comprise different additional ingredients to powders.

It can be preferred that the compositions comprise one or more other ingredient which can reduce dermatitis, or compounds which can help the healing of the skin, such as vitamins (vitamin E) and cortisone's, and also compounds to soften the skin such as vaseline, glycerin, triethyleneglycol, lanolin, paraffin and another group of polymers extensively employed by pharmaceutical and cosmetic manufactures, as also described herein.

Depending on the application of the compositions of the invention, a preferred additional ingredient can be one or more builders or dispersants. It can be preferred that a crystal growth inhibitor is present, preferably in addition to dispersants.

Suitable examples of water-soluble phosphates, suitable as crystal growth inhibitors or builders, are the alkali metal tripolyphosphates, sodium, potassium and ammonium pyrophosphate, sodium and potassium and ammonium pyrophosphate, sodium and potassium orthophosphate, sodium polymeta/phosphate in which the degree of polymerization ranges from about 6 to 21, and salts of phytic acid.

Any builder or dispersant material known in the art can be used. Particularly useful builders or dispersants can be monomeric, oligomeric and polycarboxylate-containing components,

polymeric components, borate-containing components and phosphate-containing components and silicate and aluminosilicate-containing components.

Suitable polycarboxylates or polycarboxylic acids can be succinic acid, malonic acid, (ethylenedioxy) diacetic acid, maleic acid, diglycolic acid, tartaric acid, tartaric acid and fumaric acid; citrates, aconitrates and citraconates as well as succinate derivatives such as the carboxymethyloxysuccinates described in British Patent No. 1,379,241, lactoxysuccinates described in British Patent No. 1,389,732, and aminosuccinates described in Netherlands Application 7205873, and the oxypolycarboxylate materials such as 2-oxa-1,1,3-propane tricarboxylates described in British Patent No. 1,387,447; oxydisuccinates disclosed in British Patent No. 1,261,829, 1,1,2,2-ethane tetracarboxylates, 1,1,3,3-propane tetracarboxylates and 1,1,2,3-propane tetracarboxylates; sulfosuccinate derivatives disclosed in British Patent Nos. 1,398,421 and 1,398,422 and in U.S. Patent No. 3,936,448, and the sulfonated pyrolysed citrates described in British Patent No. 1,439,000;

Polymeric components include the water soluble organic homo- or co-polymeric polycarboxylic acids or their salts in which the polycarboxylic acid comprises at least two carboxyl radicals separated from each other by not more than two carbon atoms. Polymers of the latter type are disclosed in GB-A-1,596,756. Examples of such salts are polyacrylates of MWt 1000-5000 and their copolymers with maleic anhydride, such copolymers having a molecular weight of from 2000 to 100,000, especially 40,000 to 80,000.

The polyamino components are useful herein including those derived from aspartic acid such as those disclosed in EP-A-305282, EP-A-305283 and EP-A-351629.

Terpolymers containing monomer units selected from maleic acid, acrylic acid, polyaspartic acid and vinyl alcohol, particularly those having an average molecular weight of from 5,000 to 10,000, are also suitable herein.

Other polymeric components suitable for incorporation in the compositions herein include cellulose derivatives such as methylcellulose, carboxymethylcellulose, hydroxypropylmethylcellulose and hydroxyethylcellulose.

Further useful polymeric components are the polyethylene glycols, particularly those of molecular weight 1000-10000, more particularly 2000 to 8000 and most preferably about 4000

Other preferred ingredients are amorphous or crystalline, preferably layered, silicate or aluminosilicate materials or builders. Suitable aluminosilicate zeolites have the unit cell formula  $\text{Na}_x[(\text{AlO}_2)_z(\text{SiO}_2)_y] \cdot x\text{H}_2\text{O}$  wherein  $z$  and  $y$  are at least 6; the molar ratio of  $z$  to  $y$  is from 1.0 to 0.5 and  $x$  is at least 5, preferably from 7.5 to 276, more preferably from 10 to 264. The aluminosilicate materials are in hydrated form and are preferably crystalline, containing from 10% to 28%, more preferably from 18% to 22% water in bound form.

#### Lotions, Creams, Oils, Foams, Ointments, Gels, Powders, Tablets and the like

The present compositions can be used for any suitable purpose. In particular, the present compositions are suitable for topical application to the skin or hair. In particular, the skin care compositions can be in the form of creams, sprays, lotions, gels, and the like. Preferably the cosmetic compositions herein are in the form of an oil-in-water emulsion of one or more oil phases in an aqueous continuous phase, each oil phase comprising a single oily component or a mixture of oily components in miscible or homogeneous form but said different oil phases containing different materials or combinations of materials from each other. The overall level of oil phase components in the compositions of the invention is preferably from about 0.1% to about 60%, preferably from about 1% to about 30% and more preferably from about 1% to about 10% by weight.

The present compositions preferably comprise, as either all or a portion of the oil phase or oil phases referred to above a first silicone-containing phase comprising a crosslinked polyorganosiloxane polymer and a silicone oil, wherein the composition comprises 0.1% to about 20%, preferably from about 0.5% to about 10%, more preferably from about 0.5% to about 5%, by weight of composition, of the combination of crosslinked silicone and silicone oil.

Compositions herein preferably also comprise a second non-crosslinked silicone-containing phase. In preferred embodiments the second silicone-containing phase is present in a level of from about 0.1% to about 20%, especially from about 0.1% to about 10% by weight of composition.

Suitable silicone fluids for use in the second silicone-containing phase herein include water-insoluble silicones inclusive of non-volatile polyalkyl and polyaryl siloxane gums and fluids, volatile cyclic and linear polyalkylsiloxanes, polyalkoxylated silicones, amino and quaternary ammonium modified silicones, and mixtures thereof.

In preferred embodiments the second silicone-containing phase comprises a silicone gum or a mixture of silicones including the silicone gum. As used herein, the term "silicone gum" means high molecular weight silicone-based fluids having a mass-average molecular weight in excess of about 200,000 and preferably from about 200,000 to about 400,000. Silicone oils generally have a molecular weight of less than about 200,000. Typically, silicone gums have a viscosity at 25°C in excess of about 1,000,000 mm<sup>2</sup>.s<sup>-1</sup>. The silicone gums include dimethicones as described by Petrarch and others including US-A-4,152,416, May 1, 1979 to Spitzer, et al, and Noll, Walter, Chemistry and Technology of Silicones, New York: Academic Press 1968. Also describing silicone gums are General Electric Silicone Rubber Product Data Sheets SE 30, SE 33, SE 54 and SE 76.

In preferred embodiments, another, third, oil phase is present in an amount of from about 0.1% to about 15%, more preferably from about 1% to about 10% by weight of composition. The third oil phase can be either a separate phase or can form one phase together with either or both of the first and second silicone phases. Preferably, the third oil phase is a separate phase.

This oil phase preferably comprises a non-silicone organic oil, such as a natural or synthetic oil selected from mineral, vegetable, and animal oils, fats and waxes, fatty acid esters, fatty alcohols, fatty acids and mixtures thereof, which ingredients are useful for achieving emollient cosmetic properties.

Suitable first oil phase components for use herein include, for example, optionally hydroxy-substituted C<sub>8</sub>-C<sub>50</sub> unsaturated fatty acids and esters thereof, beeswax, saturated and unsaturated fatty alcohols such as behenyl alcohol and cetyl alcohol, hydrocarbons such as mineral oils, petrolatum and squalane, fatty sorbitan esters (see US-A-3988255, Seiden, issued October 26 1976), lanolin and lanolin derivatives, animal and vegetable triglycerides such as almond oil, peanut oil, wheat germ oil, linseed oil, jojoba oil, oil of apricot pits, walnuts, palm

nuts, pistachio nuts, sesame seeds, rapeseed, cade oil, corn oil, peach pit oil, poppyseed oil, pine oil, castor oil, soybean oil, avocado oil, safflower oil, coconut oil, hazelnut oil, olive oil, grapeseed oil, shea butter, shorea butter, and sunflower seed oil and  $C_{1-24}$  esters of dimer and trimer acids such as diisopropyl dimerate, diisostearylmalate, diisostearyldimerate and triisostearyltrimerate. Of the above, highly preferred are the mineral oils, petrolatums, unsaturated fatty acids and esters thereof and mixtures thereof.

#### Amphiphilic Surfactant

A further preferred component of the compositions herein is an organic amphiphilic surfactant which is capable of forming smectic lyotropic crystals in product or when the product is being applied to the skin at ambient or elevated temperatures. Preferably the amphiphilic surfactant is capable of forming liquid crystals at a temperature in the range from about 20°C to about 40°C. Preferably the amphiphilic surfactant is capable of forming smectic lyotropic liquid crystals. Once application of the product to the skin has been completed, liquid crystals may not be identifiable on the skin surface or stratum corneum. The amphiphilic surfactant is preferably present at a level of from about 0.1% to about 20%, preferably from about 0.1% to about 10%, by weight.

Organic amphiphilic surfactants suitable for use herein include those having a weight average HLB (Hydrophilic Lipophilic Balance) in the range from about 2 to about 12, preferably from about 4 to about 8.

Preferred organic amphiphilic surfactants employed herein have a long saturated or unsaturated branched or linear lipophilic chain having from about 12 to about 30 carbon atoms such as oleic, lanolic, tetradecylic, hexadecylic, isostearyl, lauric, coconut, stearic or alkyl phenyl chains. When the hydrophilic group of the amphiphilic material forming the liquid crystal phase is a nonionic group, a polyoxyethylene, a polyglycerol, a polyol ester, oxyalkylated or not, and, for example, a polyoxyalkylated sorbitol or sugar ester, can be employed. When the hydrophilic group of the amphiphilic surfactant forming the liquid crystal phase is an ionic group, advantageously there can be used, as the hydrophilic group, a phosphatidylcholine residue as found in lecithin.

The compositions can also comprise Amphoteric, anionic, nonionic and cationic surfactants.

A wide variety of optional ingredients such as non-occlusive moisturizers, humectants, gelling agents, neutralizing agents, perfumes, colouring agents and surfactants, can be added to the skin compositions herein.

The compositions herein can comprise a humectant. Suitable humectants for use herein include sorbitol, propylene glycol, butylene glycol, hexylene glycol, ethoxylated glucose derivatives, hexanetriol, glycerine, glycine, hyaluronic acid, arginine, Ajidew (NaPCA), water-soluble polyglyceryl methacrylate lubricants and panthenols. A preferred humectant herein is glycerine (sometimes known as glycerol or glycerin). Chemically, glycerine is 1,2,3-propanetriol and is a product of commerce. One large source of the material is in the manufacture of soap.

Glycerine is especially preferred in the compositions of the invention from the viewpoint of boosting moisturisation. Also preferred for use herein is butylene glycol. Particularly preferred from the viewpoint of boosting moisturisation is a combination of glycerine and urea.

In the present compositions, the humectant is preferably present at a level of from about 0.1% to about 20%, more preferably from about 1% to about 15%, and especially from about 5% to about 15% by weight of composition.

The compositions of the invention can also contain a hydrophilic gelling agent at a level preferably from about 0.01% to about 10%, more preferably from about 0.02% to about 2%, and especially from about 0.02% to about 0.5%. The gelling agent preferably has a viscosity (1% aqueous solution, 20°C, Brookfield RVT) of at least about 4000 mPa.s, more preferably at least about 10,000 mPa.s and especially at least 50,000 mPa.s.

Suitable hydrophilic gelling agents can generally be described as water-soluble or colloiddally water-soluble polymers, and include cellulose ethers (e.g. hydroxyethyl cellulose, methyl cellulose, hydroxypropylmethyl cellulose), polyvinylpyrrolidone, polyvinylalcohol, guar gum, hydroxypropyl guar gum and xanthan gum.

Preferred hydrophilic gelling agents herein, however, are acrylic acid/ethyl acrylate copolymers and the carboxyvinyl polymers sold by the B.F. Goodrich Company under the trade mark of



Carbopol resins. These resins consist essentially of a colloiddally water-soluble polyalkenyl polyether crosslinked polymer of acrylic acid crosslinked with from 0.75% to 2.00% of a crosslinking agent such as for example polyallyl sucrose or polyallyl pentaerythritol. Examples include Carbopol 934, Carbopol 940, Carbopol 950, Carbopol 954, Carbopol 980, Carbopol 951 and Carbopol 981. Carbopol 934 is a water-soluble polymer of acrylic acid crosslinked with about 1% of a polyallyl ether of sucrose having an average of about 5.8 allyl groups for each sucrose molecule. A most preferred polymer is Carbopol 954. Also suitable for use herein are hydrophobically-modified cross-linked polymers of acrylic acid having amphipathic properties available under the Trade Name Carbopol 1382, Carbopol 1342 and Pemulen TR-1 (CTFA Designation: Acrylates/10-30 Alkyl Acrylate Crosspolymer). A combination of the polyalkenyl polyether cross-linked acrylic acid polymer and the hydrophobically modified cross-linked acrylic acid polymer is also suitable and is preferred for use herein. The gelling agents herein are particularly valuable for providing excellent stability characteristics over both normal and elevated temperatures.

Neutralizing agents suitable for use in neutralizing acidic group containing hydrophilic gelling agents herein include sodium hydroxide, potassium hydroxide, ammonium hydroxide, monoethanolamine, diethanolamine and triethanolamine.

Other optional materials include keratolytic agents/desquamation agents such as salicylic acid; proteins and polypeptides and derivatives thereof; water-soluble or solubilizable preservatives preferably at a level of from about 0.1% to about 5%, such as Germall 115, methyl, ethyl, propyl and butyl esters of hydroxybenzoic acid, benzyl alcohol, EDTA, Euxyl (RTM) K400, Bronopol (2-bromo-2-nitropropane-1,3-diol) and phenoxypropanol; anti-bacterials such as Irgasan (RTM) and phenoxyethanol (preferably at levels of from 0.1% to about 5%); soluble or colloiddally-soluble moisturising agents such as hyaluronic acid and starch-grafted sodium polyacrylates such as Sanwet (RTM) IM-1000, IM-1500 and IM-2500 available from Celanese Superabsorbent Materials, Portsmouth, VA, USA and described in USA-A-4,076,663; vitamins such as vitamin A, vitamin C, vitamin E and vitamin K; alpha and beta hydroxyacids; aloe vera; sphingosines and phytosphingosines, cholesterol; skin whitening agents; N-acetyl cysteine; colouring agents; perfumes and perfume solubilizers and additional surfactants/emulsifiers such as fatty alcohol ethoxylates, ethoxylated polyol fatty acid esters, wherein the polyol can be selected from glycerine, propyleneglycol, ethyleneglycol, sorbitol, sorbitan,

polypropyleneglycol, glucose and sucrose. Examples include glyceryl monohydroxy stearate and stearyl alcohol ethoxylated with an average of from 10 to 200 moles of ethylene oxide per mole of alcohol and PEG-6 caprylic/capric glycerides.

The compositions of the present invention can also comprise a safe and effective amount of vitamins, such as vitamin E, B, preferably vitamin B<sub>3</sub> vitamin A or retinoid. The compositions of the present invention preferably comprise from about 0.01% to about 50%, more preferably from about 0.1% to about 10%, even more preferably from about 0.5% to about 10%, and still more preferably from about 1% to about 5%, most preferably from about 2% to about 5%, of the vitamin.

The pH of the compositions is preferably from about 4 to about 9, more preferably from about 6 to about 8.0.

The balance of the composition is water or an aqueous carrier suitable for topical application to the skin. The water content of the compositions herein is generally from about 30% to about 98.89%, preferably from about 50% to about 95% and especially from about 60% to about 90% by weight.

The compositions of the invention are preferably in the form of a moisturising cream or lotion, which can be applied to the skin as a leave-on product.

Claims

1. A composition for the reduction of the enzyme activity, comprising ethylene diamine disuccinic acid or salts thereof (EDDS) complexing agent.
2. An aqueous composition for the reduction of the enzyme activity which comprises a complexing agent, and which in use comprises calcium ions and one or more metal ions, selected from the group consisting of Cu, Fe, Zn, Ni, Co, whereby the  $-\log_{10}C_T$  is equal to or greater than the smallest value of A or B, wherein

$$A \text{ is } -\log_{10}(L_T - M_T) \text{ and } B \text{ is } K_1(1 - K_2\sqrt{I})(1 - K_3.\exp(-K_4.P)),$$

$C_T$  is the total concentration of calcium ions,  $L_T$  is the total concentration of complexing agent,  $M_T$  is the total concentration of the metal ions, selected from the group consisting of Cu, Fe, Zn, Ni and Co;  $P$  is the pH of the composition,  $I$  is the ionic strength of the composition in moles/ litre, where  $K_1$ ,  $K_2$ ,  $K_3$  and  $K_4$  are the following constants for the metals ions:

	Cu <sup>++</sup>	Fe <sup>+++</sup>	Zn <sup>++</sup>	Ni <sup>++</sup>	Co <sup>++</sup>
K1	11.062	5.754	7.963	13.098	7.642
K2	0.496	0.479	0.619	0.535	0.652
K3	2.479	9385.0	24.202	1.473	32.069
K4	0.227	1.092	0.506	0.126	0.532

3. A composition according to claim 1 or 2, for the reduction of the enzyme activity of enzymes in contact with the human or animal body.
4. Use of ethylene diamine disuccinic acid or salts thereof (EDDS) for preparation of a composition for reduction of the enzyme activity, preferably of enzymes in contact with the human or animal body.

5. Use of a complexing agent for preparation of an aqueous composition for reduction of the enzyme activity, preferably of enzymes in contact with the human or animal body, which in use comprises calcium ions and one or more metal ions, selected from the group consisting of Cu, Fe, Zn, Ni, Co, whereby the  $-\log_{10} C_T$  is equal to or greater than the smallest value of A or B, wherein

$$A \text{ is } -\log_{10}(L_T - M_T) \text{ and } B \text{ is } K_1(1 - K_2\sqrt{I})(1 - K_3 \cdot \exp(-K_4 \cdot P)),$$

$C_T$  is the total concentration of calcium ions,  $L_T$  is the total concentration of complexing agent,  $M_T$  is the total concentration of the metal ions, selected from the group consisting of Cu, Fe, Zn, Ni and Co; P is the pH of the composition, I is the ionic strength of the composition, wherein all concentrations are in moles/ litre, where  $K_1$ ,  $K_2$ ,  $K_3$  and  $K_4$  are the following constants for the metals ions:

	Cu <sup>++</sup>	Fe <sup>+++</sup>	Zn <sup>++</sup>	Ni <sup>++</sup>	Co <sup>++</sup>
K1	11.062	5.754	7.963	13.098	7.642
K2	0.496	0.479	0.619	0.535	0.652
K3	2.479	9385.0	24.202	1.473	32.069
K4	0.227	1.092	0.506	0.126	0.532

6. A composition according to any of claims 2, being an aqueous composition, obtainable by a process comprising the step of addition of the complexing agent to an aqueous solution, comprising calcium ions and the metal ions selected from the group consisting of Cu, Fe, Zn, Ni, Co.
7. A composition according to any of claims 1 to 4, wherein the complexing agent is EDDS, present at a level of from 0.001% to 30% by weight of the composition.
8. A composition according to any preceding claim for reduction of the enzyme activity of enzymes present in the body exudates.

9. A composition according to any preceding claim for reduction of the activity of lipase enzymes.
10. A composition according to any of claim 1, 2 or 3, comprising in use calcium ions and metal ions selected from Fe, Cu, Co, Zn and Ni.
11. A composition according to any preceding claim in the form of a spray, cream, spray, foam, lotion, gel, oil, ointment or powder.
12. An absorbent article, preferably a wipe or a diaper, comprising the composition according to any preceding claim.
13. A deodorant comprising the composition according to any preceding claim.
14. Use of a composition according to any preceding claim for the reduction of the enzyme activity, preferably of enzymes in contact with the human or animal body.
15. Use of a composition according to any of claims 1 to 13 for treatment of enzymatic dermatitis.
16. Use of a composition according to any of claims 1 to 13 for treatment of malodour of the body.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IB 99/00120

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K7/48 A61K7/32 A61K7/11

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 44006 A (CIBA GEIGY AG ;BACHMANN FRANK (DE); EHLIS THOMAS (DE); OCHS DIETMA) 27 November 1997 formula 2 see page 4; claims 6,9,10,13,14; examples 3-5 ---	1-16
Y	EP 0 811 390 A (PROCTER & GAMBLE) 10 December 1997 see page 3, line 5-30; claim 5 ---	1-16
X,P	US 5 846 925 A (CRUMP DRUCE K ET AL) 8 December 1998 see abstract see column 4, line 30-62 see column 6, line 28-44; claim 6 --- -/-	1-16

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex

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## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/IB 99/00120

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 288 812 A (PROCTER & GAMBLE) 1 November 1995 see abstract see page 18; example 4 ---	1-16
X	NISHIKIORI T ET AL: "PRODUCTION BY ACTINOMYCETES OF (S,S)-N,N-ETHYLENEDIAMINE -DISUCCINICACID, AN INHIBITOR OF PHOSPHOLIPASE C" JOURNAL OF ANTIBIOTICS, vol. 37, April 1984, page 426/427 XP000615485 ---	1,3,4,8, 9,14-16
Y	see abstract; table 1 ---	1-16
A	WO 97 40827 A (ANALYTICON AG BIOTECHNOLOGIE P ;DOERR HANS WILHELM (DE); BINDSEIL) 6 November 1997 see abstract; claim 4 ---	1-16
Y	see page 1, paragraph 2 ---	1,3,4,8, 9,14-16
A	TAKAHASHI R. ET AL: "Biodegradabilites of Ethylenediamine-N,N'-disuccinic acid (EDDS) and other chelating agents" BIOSCI. BIOTECH. BIOCHEM, vol. 61, no. 11, 1997, pages 1957-1959, XP002096204 see page 1957, paragraph 4; figure 1 ---	1-16
Y	WO 96 01804 A (ALBEMARLE CORP) 25 January 1996 see abstract ---	1-16
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Information on patent family members

International Application No  
PCT/IB 99/00120

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EP 0811390	A	10-12-1997	AU 3147197 A AU 3287697 A EP 0811392 A WO 9746191 A WO 9746194 A	05-01-1998 05-01-1998 10-12-1997 11-12-1997 11-12-1997
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GB 2288812	A	01-11-1995	NONE	
WO 9740827	A	06-11-1997	DE 19616992 C AU 2772997 A CA 2252779 A	11-09-1997 19-11-1997 06-11-1997
WO 9601804	A	25-01-1996	US 5550285 A EP 0770057 A JP 10502635 T	27-08-1996 02-05-1997 10-03-1998





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(54) Title: AQUEOUS COMPOSITIONS COMPRISING COMPLEXING AGENTS AND USES THEREOF

## (57) Abstract

The invention relates to aqueous compositions, comprising calcium ions and metal ions selected from the group comprising Cu, Fe, Zn, Ni and Co, and a specific complexing agent and applications for these aqueous compositions.

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## AQUEOUS COMPOSITIONS COMPRISING COMPLEXING AGENTS AND USES THEREOF

### Technical Field

The invention relates to aqueous compositions comprising calcium ions and metal ions selected from the group comprising Cu, Fe, Zn, Ni and Co, and a specific complexing agent.

The invention also relates to the use of a specific complexing agent for selectively complexing selected metal ions, in the presence of calcium ions.

### Background to the Invention

In a variety of technical fields the presence of certain metal ions such as heavy metal ions is undesirable because it is known that they can adversely affect the performance of various technical processes. In general, chelating or complexing agents are used to ameliorate this problem.

For example, in pulp, paper or textile bleaching or de-inking, metal ions tend to reduce the efficiency of the bleaching process and also tend to produce colour in the paper (or textile) product, iron ions being the most detrimental to achieving brightness. The bleaching processes are enhanced through the use of chelants or sequesterants that inactivate metal ions. However, a problem can be that these chelants are not bleach stable, in particular when oxidative bleaches are used. The most well-known chelants are aminomethylene carboxylates, such as NTA and EDTA and their salts.

The presence of certain metal ions can be detrimental in other technical fields. For example in dyeing processes, certain dyestuffs are detrimentally affected by various metals, especially alkaline-earth metals or heavy metals such as iron and copper, which

can be accidentally present in the dyeing bath. These metals have the effect of causing agglomeration or flocculation of the dyestuff, modifications of tone and depth of colour, a decrease in the transfer of dye to the textile fibres and a reduction in the fixation of the dyestuff to the fibre. To reduce the negative impact of these metals upon the physical and colouring properties of a dyestuff, complexing agents are used, for example polyphosphate complexing agents, to render ineffective certain metal ions.

In food products, various ingredients are not stable to oxidation and the products can become rancid upon storage. It is known that the oxidation process is catalysed by certain metal ions. Thus, various chelating agents are commonly employed to reduce the catalytic activity of these metal ions and to improve the stability of the ingredients, for example citric acid and ascorbic acid. Metal ions may also adversely affect the performance of yeast.

In other technical fields, the presence of certain metal ions such as heavy metal ions is actually needed and a controlled delivery of metal ions or a control-system to maintain a certain amount of metal ions can be essential to the well-functioning of these applications. For example, in methods of magnetic resonance imaging, delivery of specific metal ions in the human body is needed; in (waste) water treatment, certain metal ions are needed to inhibit algae growth; in methods for electroless plating, metal ions are required to plate metal surfaces; in scale removal processes where not only metal ions have to be removed but also metal oxides can be used to form a coating on the surface, to avoid scale deposition; in agricultural processes to deliver nutrients to the plants; in tanning processes, certain metal ions are required to provide the tanning; In these technical fields, chelating or complexing agents are useful to improve the efficiency of the techniques or processes.

Furthermore, it is known that certain metal ions can cause health or cosmetic problems, for example for example nickel dermatitis and heavy metal poisoning (either by accidental intake of metal ions, or by absorption of iron ions from the cells by failure of

certain body functions); certain enzymatic reactions, which require the presence of certain metal ions, can cause cosmetic or health problems.

Thus, on one hand, it has been a challenge to reduce the negative effects of metal ions and on the other hand, to improve the benefits obtainable by the use of metal ions and therefor, a variety of chelating or complexing agents are developed which can chelate the metal ions.

In the past decades, the main aim has been to develop chelating agents which have an improved binding capacity for heavy metal ions. Well-known chelating agents thereto are, for example, EDTA and DTPA.

The inventors now have found that even those chelating agents which have a very high binding capacity for heavy metal ions, do not always perform very effectively.

The inventors have now found that this can be due to the fact that these chelating agents do not just have a high binding capacity for heavy metal ions, but also for other metal ions which may be present. It has been found that, for example, the presence of calcium ions can reduce the efficiency or effectiveness of certain chelating agents.

The nature of a variety of systems or applications where heavy metal chelating agents are useful, is often such that the presence of calcium ions is unavoidable or even needed. For example, in bleaching, dyeing or tanning processes, large quantities of untreated water may comprise high levels of calcium ions, are used, which can thus affect the heavy metal-chelating capacity of these chelants, when used in these processes; in water reservoirs, in particularly waste-water reservoirs, pools, lakes, irrigation systems etc., high levels of calcium ions are unavoidable; in metal scale removal and metal plating processes, large quantities of calcium ions can be present; in the human body, calcium is present which will have a negative affect on the performance of chelating agents used in treatments; in food products, in particular dairy products, large quantities of calcium are

present, which can reduce the efficiency of commonly used chelating agents, used as preservatives or anti-oxidants, to prevent the food ingredients to oxidise and become rancid. In fermentation processes, it has been found that the presence of calcium ions can be required for the performance of the yeast, whilst the presence of other metal ions is detrimental to the yeast performance, which thus need to be removed.

However, the inventors have now found a solution thereto. They have now found that specific complexing agents are very effective, specific complexing agents for certain metal ions, namely Cu, Fe, Zn, Ni and Co, but not for calcium ions. Thus, these specific agents are very effective complexing agents in technical applications, whereby the presence of calcium is unavoidable or even essential and whereby complexing of specific metal ions is required or whereby delivery of specific, chelated metal ions is required.

### Summary of the Invention

The invention provides aqueous composition of the invention, comprising calcium ions, preferably when in use, and one or more metal ions, selected from the group consisting of Cu, Fe, Zn, Ni and Co and comprising a complexing agent, are those whereby -  $\log_{10}C_T$  is equal to or greater than the smallest value of A or B, where

$$A \text{ is } -\log_{10}(L_T - M_T) \text{ and } B \text{ is } K_1(1 - K_2\sqrt{I})(1 - K_3.\exp(-K_4.P)),$$

wherein  $C_T$  is the total concentration of calcium ions,  $L_T$  is the total concentration of complexing agent,  $M_T$  is the total concentration of the metal ions, selected from the group consisting of Cu, Fe, Zn, Ni and Co; P is the pH of the composition, I is the ionic strength of the composition, where  $K_1$ ,  $K_2$ ,  $K_3$  and  $K_4$  are the following constants for the metals ions:

	Cu <sup>++</sup>	Fe <sup>+++</sup>	Zn <sup>++</sup>	Ni <sup>++</sup>	Co <sup>++</sup>
K1	11.062	5.754	7.963	13.098	7.642

K2	0.496	0.479	0.619	0.535	0.652
K3	2.479	9385.0	24.202	1.473	32.069
K4	0.227	1.092	0.506	0.126	0.532

All concentrations in the above equation are measured as moles/ litre.

The invention also relates to specific applications for these aqueous compositions, whereby the use of specific complexing agents amounts to the selectively chelating of one or more metal ions, selected from the group comprising Cu, Fe, Zn, Ni and Co, in the presence of calcium ions.

#### Detailed Description of the Invention

##### Aqueous Compositions

The aqueous compositions of the invention are defined by a specific pH, the presence of a specific concentration of calcium ions and the presence of specific levels of metal ions, selected from the group Cu, Fe, Zn, Ni and Co (herein referred to as selected metal ions), and a specific level of complexing agents, such that the chelating agent selectively will complex the metal ions.

Said aqueous composition can be obtainable by a process comprising the step of addition of a complexing composition comprising a complexing agent and optionally other compounds, to an aqueous solution, comprising calcium ions.

Depending on the application, the aqueous composition according to the invention may contain the selected metal ions and the calcium ions or may contain the selected metal ions and calcium ions in use

It may be preferred that the selected metal ions in the compositions are chelated or 'complexed' by the complexing agent, thereby preferably forming a complex.

However, it may be preferred that the complexing agent in the compositions is substantially free from these selected metal ions and that in use, the selected metal ions are chelated or 'complexed' by the complexing agent, thereby preferably forming a complex.

When nickel and/ or copper ions are present in the composition, it can be preferred that the composition has a pH of 4 or more. When zinc ions are present in the composition, it can be preferred that the composition has a pH of 7 or more. When iron ions are present in the composition, it can be preferred that the composition has a pH of 9.5 or more.

The aqueous composition is preferably not a composition for use in laundry or dish washing processes or a composition for use in photography or photo-development processes.

It should be understood that for the purpose of the invention and depending on the application of the composition, the calcium ions and optionally the selected metal ions can be present in the compositions to be used in the applications described herein, or the calcium ions and optionally the selected metal ions can be present in the compositions, when in use in the applications.

Furthermore, the levels of incorporation of the complexing and the amounts of calcium ions and selected metal ions will depend on the application of the compositions of the invention. Depending on the application, it may be preferred that the complexing agent and the selected metal ion are present in a stoichiometric amounts, or that one of the components is present in a stoichiometric excess.

#### Process for Preparation of the Compositions



The aqueous composition can be prepared by a process, comprising the step of addition of a complexing composition, comprising a complexing agent, to an aqueous mixture, comprising calcium ions, whereby the complexing composition comprises one or more of the selected metal ions selected. The complexing agent and the selected metal ions can be added to the complexing composition either separately or as a premix composition, in which they may be complexed.

Alternatively, the aqueous composition can be prepared by a process comprising the step of addition of a complexing composition, comprising a complexing agent, to an aqueous mixture, comprising calcium ions, whereby the aqueous mixture also comprises one or more of the selected metal ions.

Depending on the application of the aqueous composition and the process for preparing the composition, the selected metal ions can have any counterion, preferably sulphate or chorine, and they can be present in the form of alkali metal or ammonium salts.

#### Complexing Agents.

A highly preferred complexing agent for use in aqueous compositions of the invention is N, N' ethylene diamine disuccinic acid or its salt (EDDS).

It is known that the (S,S) EDDS isomer is more readily biodegradable than the (R,R) isomer. Thus, depending of the application of the aqueous compositions of the invention, it may be desirable to use only one of the isomers of EDDS. It may be preferred that a racemic mixture of the isomers is used in the aqueous compositions, for example because the racemic mixture is less expensive.

The use of EDDS in the compositions of the invention has as an additional benefit that EDDS is very stable, in particular in bleach containing compositions, and that EDDS can

be easily and readily separated from the selected metal ions, when necessary, by formation of cyclic EDDS under specific reaction conditions.

For the purpose of the invention and depending on the application of the aqueous composition, it should be understood that either the complexing agent can be introduced in the composition comprising the selected metal ions, to selectively form a complex with these metal ions, or the complexing agent can comprise one or more of the selected metal ions, prior to introduction into the composition (which can additionally contain one or more of the selected metal ions).

#### pH Measurement

The pH as used herein can be determined by any known method of calculating or measuring the pH of an aqueous solution.

#### Ionic Strength Measurement

The ionic strength (I) can be determined by the following equation:

$$I = \frac{1}{2} \sum c_i z_i^2,$$

wherein c is the molecular concentration of the soluble ion (i) and z is the charge of the soluble ion (i).

#### Additional Ingredients

The aqueous composition of the invention will preferably comprise additional ingredients. The precise nature of the additional ingredients and the levels thereof will depend on the purpose or application of the aqueous composition.

Depending on the application of the compositions of the invention, a preferred additional ingredient can be one or more builders or dispersants. It can be preferred that a crystal growth inhibitor is present, preferably in addition to dispersants.

Suitable examples of water-soluble phosphates, suitable as crystal growth inhibitors or builders, are the alkali metal triphosphates, sodium, potassium and ammonium pyrophosphate, sodium and potassium and ammonium pyrophosphate, sodium and potassium orthophosphate, sodium polymeta/phosphate in which the degree of polymerization ranges from about 6 to 21, and salts of phytic acid.

Any builder or dispersant material known in the art can be used. Particularly useful builders or dispersants can be monomeric, oligomeric and polycarboxylate-containing components, polymeric components, borate-containing components and phosphate-containing components and silicate and aluminosilicate-containing components.

Suitable polycarboxylates or polycarboxylic acids can be succinic acid, malonic acid, (ethylenedioxy) diacetic acid, maleic acid, diglycolic acid, tartaric acid, tartronic acid and fumaric acid; citrates, aconitrates and citraconates as well as succinate derivatives such as the carboxymethyloxysuccinates described in British Patent No. 1,379,241, lactoxysuccinates described in British Patent No. 1,389,732, and aminosuccinates described in Netherlands Application 7205873, and the oxypolycarboxylate materials such as 2-oxa-1,1,3-propane tricarboxylates described in British Patent No. 1,387,447; oxydisuccinates disclosed in British Patent No. 1,261,829, 1,1,2,2-ethane tetracarboxylates, 1,1,3,3-propane tetracarboxylates and 1,1,2,3-propane tetracarboxylates; sulfosuccinate derivatives disclosed in British Patent Nos. 1,398,421 and 1,398,422 and in U.S. Patent No. 3,936,448, and the sulfonated pyrolysed citrates described in British Patent No. 1,439,000;

Polymeric components include the water soluble organic homo- or co-polymeric polycarboxylic acids or their salts in which the polycarboxylic acid comprises at least two carboxyl radicals separated from each other by not more than two carbon atoms. Polymers of the latter type are disclosed in GB-A-1,596,756. Examples of such salts are polyacrylates of MWt 1000-5000 and their copolymers with maleic anhydride, such copolymers having a molecular weight of from 2000 to 100,000, especially 40,000 to 80,000.

The polyamino components are useful herein including those derived from aspartic acid such as those disclosed in EP-A-305282, EP-A-305283 and EP-A-351629.

Terpolymers containing monomer units selected from maleic acid, acrylic acid, polyaspartic acid and vinyl alcohol, particularly those having an average molecular weight of from 5,000 to 10,000, are also suitable herein.

Other polymeric components suitable for incorporation in the compositions herein include cellulose derivatives such as methylcellulose, carboxymethylcellulose, hydroxypropylmethylcellulose and hydroxyethylcellulose.

Further useful polymeric components are the polyethylene glycols, particularly those of molecular weight 1000-10000, more particularly 2000 to 8000 and most preferably about 4000

Other preferred ingredients are amorphous or crystalline, preferably layered, silicate or aluminosilicate materials or builders. Suitable aluminosilicate zeolites have the unit cell formula  $\text{Na}_z[(\text{AlO}_2)_z(\text{SiO}_2)_y] \cdot x\text{H}_2\text{O}$  wherein  $z$  and  $y$  are at least 6; the molar ratio of  $z$  to  $y$  is from 1.0 to 0.5 and  $x$  is at least 5, preferably from 7.5 to 276, more preferably from 10 to 264. The aluminosilicate materials are in hydrated form and are preferably crystalline, containing from 10% to 28%, more preferably from 18% to 22% water in bound form.

### Applications

The aqueous compositions are applicable in a variety of applications, where calcium ions are present and selective complexing or binding of the selected metal ions is required. Examples, thereof are bleaching or deinking processes for pulp or paper and bleaching processes for textiles, such as oxidative bleaching and chlorine-based bleaching or in particular reductive bleaching; dyeing processes of pulp, paper and textiles; algae, fungi and bacterial growth stabilisation or inhibition; (electroless) plating or finishing of metal surfaces; removal of metal from waste-water or sludge; metal scale removal; tanning processes such as used in leather manufacturing processes; rubber manufacturing processes; food preparation processes, in particular food preservation processes, in particular for food which is rich in calcium, which is sensitive to oxidation, such as lipid- or protein-containing products; fermentation processes such as used by the production of yoghurt or wine and beer, in particular the wine- or beer-clarification process step thereof; agricultural processes for delivering nutrients to plants; methods for reduction of the enzyme activity of enzymes present on the human skin, including treatment of enzymatic dermatitis; methods for treatment of metal poisoning, such as treatment of metal dermatitis and chelation therapy; and methods for delivering metal ions to the human or animal body or to plants, such as delivering of plant nutrients and methods of Magnetic Resonance Imaging (MRI).

These applications will now be discussed in more detail.

### Reductive Bleaching/ De-inking

The process of preparation of the aqueous compositions of the invention, comprising the step of addition of a complexing composition, comprising a complexing agent, to an aqueous solution, comprising calcium ions and one or more of the selected metal ions,

can be part of a reductive bleaching or de-inking process, in particular for cellulosic material such as a cotton, pulp or paper.

Thus, one of the preferred processes wherein the aqueous compositions of the invention can be used are reductive pulp- or paper- or textile-bleaching or de-inking processes.

The reductive bleaching process comprises the step of contacting the pulp, paper or textile with the aqueous composition of the invention, containing the reductive bleaching agent.

The preferred complexing agent of the compositions for use in the bleaching processes is EDDS. The amount of complexing agent employed, may vary in accordance with the nature of the process. Generally, at least 0.001% by weight of the dry pulp of a complexing agent or component is present, more preferably at least 0.01%.

In the reductive bleaching process, large quantities of water are used. Therefore, the calcium ion concentration will generally be determined by the hardness of the used water.

The most preferred reductive bleaching process herein, is a bleaching process for bleaching (deinked) pulp, which uses reductive bleaching agent containing a reducing agent and a bleaching agent, preferably a sulfite or dithionite-based agent. The dithionite ion ( $S_2O_4^{2-}$ ), thereby provided, is then the active bleaching species. Preferably, the reducing agent more electronegative than the sulfite ion, in a medium initially having a pH ranging from 6 to 12. The reducing agent that is more electronegative than the sulfite ion, hereinafter designated the "reducing agent" is preferably selected from among thiourea dioxide or formamidine sulfinic acid, sodium borohydride and sodium hydrosulfite.

Dithionite is typically provided to the bleaching process in one of three manners: A) a dithionite-based product in dry form may be dissolved and added to the compositions of the invention and then to a the pulp slurry or textile, B) commercial dithionite solutions products (which have limited storage stabilities) can be added to the compositions of the invention and then to the pulp slurry or textile, or C) dithionite may be generated on-site from sodium borohydride, sodium hydroxide and an available  $S^{4+}$  species, such as  $SO_2$ , waste  $HSO_3^-$  or  $HSO_3^-/SO_2$  solution. The chemistry and cycle of an on-site dithionite generation is described, for example, in "Hydrosulfite Bleaching" by R. Barton, C. Tredway, M. Elles & E. Sullivan, Pulp and Paper Manufacture, 3<sup>rd</sup> Edition, Volume 2, Mechanical Pulping, R.A. Leask (Ed.) Tappi/CPPA Joint Textbook Committee of the Paper Industry (1987).

Suitable alkali metal hydrosulfites include sodium hydrosulfite, potassium hydrosulfite, lithium hydrosulfite, and mixtures thereof. Highly preferred can be zinc derived sodium dithionites, as described in US patent 3,985,674. While available in the anhydrous form, alkali metal hydrosulfites (dithionites) are advantageously used in a solution. Sodium hydrosulfite bleach solutions are produced by various processes, but they commonly involve the reduction of sodium bisulfite solutions, preferably at pH levels around 6.

The amount of reducing agent employed may vary in accordance with the nature of the process. For example, in the case of thiourea dioxide or dithionite, the amount ranges from 0.1% to 5% by weight of the pulp or textile in the dry state. Sodium borohydride is used in proportions of approximately 0.01% to 0.5% by weight of the pulp or textile in the dry state, typically ranging from 0.05% to 0.25%.

The amount of sulfite-bleaching agent employed is preferably greater than 0.1% by weight of the pulp or textile in the dry state. For example, in the process herein, at least 0.25 and preferably 0.5% to 1.5% by weight of the dry pulp or textile, of sodium dithionite is used.

The compositions used in the bleaching-processes in accord with the invention, preferably comprise a bleaching antioxidant, preferably selected from the group

consisting of ascorbic acid and palmitoyl ascorbate, is brighter than pulp bleached with dithionite blends only or peroxide only. These antioxidants can be effectively added to the process before the bleaching agent is added to the pulp or textile or simultaneously with the bleaching agent bleached.

The reducing agent is conveniently employed in the form of an aqueous solution thereof, for example a solution of 12% by weight of sodium borohydride marketed under the trademark BOROL.RTM. by the Ventron Corporation.

A typical composition in accord of the invention, used in the bleaching process of the invention, comprises from 1% to 3.6% EDDS sodium salt 6% to 15% NaBH<sub>4</sub>, 15% to 35% NaOH., and 1.5% to 7% sodium dithionite.

The use of the compositions of the invention leads to a very effective or efficient bleaching, an reduced fabric or paper damage, and a reduced dingy or yellow appearance of the fabric or paper

#### Oxidative Bleaching/ De-inking

The process of preparation of the aqueous compositions of the invention, comprising the step of addition of a complexing composition, comprising a complexing agent, to an aqueous solution, comprising calcium ions and one or more of the selected metal ions, can be part of oxidative bleaching or de-inking process for cellulosic material such as a cotton, pulp or paper.

Thus, the aqueous compositions of the invention can be used in an oxidative pulp- or paper- or textile-bleaching or de-inking process, which preferably comprises the step of contacting the pulp, paper or textile with the aqueous composition of the invention, containing the oxidative bleaching agent.

The preferred oxidative bleaching agent contains a peroxide source, such hydrogen peroxide. Inorganic perhydrate salts are a preferred source of hydrogen peroxide, which



are normally used in the bleaching process, in the form of the alkali metal, preferably sodium salt at a level of from 0.05% to 20% by weight, more preferably from 1% to 15% by weight and most preferably from 2% to 8% by weight of the pulp, paper or textile.

Examples of inorganic perhydrate salts include perborate, percarbonate, perphosphate, persulfate, preferably potassium peroxymonopersulfate, and persilicate salt. Sodium perborate can be in the form of the monohydrate of nominal formula  $\text{NaBO}_2\text{H}_2\text{O}_2$  or the tetrahydrate  $\text{NaBO}_2\text{H}_2\text{O}_2 \cdot 3\text{H}_2\text{O}$ . Sodium percarbonate has a formula corresponding to  $2\text{Na}_2\text{CO}_3 \cdot 3\text{H}_2\text{O}_2$ , and is available commercially as a crystalline solid.

In the bleaching process, large quantities of water are used. Therefore, the calcium ion concentration will generally be determined by the hardness of the used water.

The preferred complexing agent of the compositions for use in the bleaching processes is EDDS, which has been found to be a very specific and effective complexing agent in the presence of calcium. The amount of complexing agent employed, may vary in accordance with the nature of the process. Generally, at least 0.001% by weight of the dry pulp of a complexing agent or component is present, more preferably at least 0.01%.

An additional advantage of the use of EDDS as complexing agent in an oxidative bleaching process herein, is that EDDS is very stable in the presence of oxygen bleach.

The process can comprise the step of addition of the paper, pulp or textile to a solution containing a alkaline buffer (e.g.  $\text{NaOH}$ ) and sodium silicate, whereto the bleach and the complexing agent are added. It can be preferred however, to add a acidity source (e.g.  $\text{H}_2\text{SO}_4$  or  $\text{H}_2\text{SO}_3$ ) to the paper, pulp or textile, prior to addition of the bleach and the complexing agent.

Additionally, chlorine-base bleach can be present.

Chlorine-Based Bleaching/ De-inking

The process of preparation of the aqueous compositions of the invention, comprising the step of addition of a complexing composition, comprising a complexing agent, to an aqueous solution, comprising calcium ions and one or more of the selected metal ions, can be part of chlorine-based bleaching or de-inking process for cellulosic material such as a cotton, pulp or paper.

Thus, the aqueous compositions of the invention can be used in a chlorine-based pulp- or paper- or textile-bleaching or de-inking process, which preferably comprises the step of contacting the pulp, paper or textile with the aqueous composition of the invention, containing the chlorine-based bleaching agent.

Depending on the application, the chlorine-based bleaching agent is typically present at a level of from 0.05% to 20% by weight, more preferably from 1% to 15% by weight and most preferably from 2% to 8% by weight of the pulp, paper or textile.

In the bleaching process, large quantities of water are used. Therefore, the calcium ion concentration will generally be determined by the hardness of the used water.

The preferred complexing agent of the compositions for use in the bleaching processes is EDDS, which has been found to be a very specific and effective complexing agent in the presence of calcium. The amount of complexing agent employed, may vary in accordance with the nature of the process. Generally, at least 0.001% by weight of the dry pulp of a complexing agent or component is present, more preferably at least 0.01%.

The chlorine-based bleach is such that a hypochlorite species is formed in aqueous solution. The hypochlorite ion is chemically represented by the formula  $\text{OCl}^-$ .

Those bleaching agents which yield a hypochlorite species in aqueous solution include alkali metal and alkaline earth metal hypochlorites, hypochlorite addition products, chloramines, chlorimines, chloramides, and chlorimides. Specific examples of compounds of this type include sodium hypochlorite, potassium hypochlorite, monobasic calcium hypochlorite, dibasic magnesium hypochlorite, chlorinated trisodium phosphate dodecahydrate, potassium dichloroisocyanurate, sodium dichloroisocyanurate sodium dichloroisocyanurate dihydrate, trichlorocyanuric acid, 1,3-dichloro-5,5-dimethylhydantoin, N-chlorosulfamide, Chloramine T, Dichloramine T, chloramine B and Dichloramine B. A preferred bleaching agent for use herein of the instant invention is sodium hypochlorite, potassium hypochlorite, or a mixture thereof. A preferred chlorine-based bleach can be Triclosan (trade name).

Most of the above-described hypochlorite-yielding bleaching agents are available in solid or concentrated form and are dissolved in water during preparation of the compositions of the invention. Some of the above materials are available as aqueous solutions and are as such added to the process or the aqueous composition of the invention.

#### Electroless Plating/ Corrosion Protection

The processes of preparation of the aqueous compositions of the invention can be part of a process for electroless plating.

Thus, the aqueous solutions of the invention can also be used in a process for electroless plating of metal surfaces, whereby calcium ions are present.

In general, the process comprises contacting a metal surface with the aqueous solution. Thus, a preferred process comprises the step of placing a metal surface in an aqueous solution of the invention, preferably comprising, as (one of) the selected metal ions, copper or zinc ions.

In a preferred process, , for example copper ions are reduced at the metal surface/solution interface and then deposited on the metal surface. In this preferred process, the used aqueous solution in accord with the invention, comprises a complexing agent which selectively binds those metal ions which need to be reduced for plating. This can be useful to prevent or reduce metal hydroxide precipitates forming and to buffer the amount of metal ions available for reduction, thus obtaining an effective and even plating. Any reduction method or reduction agent can be used in the process of the invention to reduce the metal ions.

In another preferred embodiment, the metal ions, preferably in the form of a metal salt, such as zinc salt, is present in the composition of the invention, and the complexing agent selectively forms a complex with the metal ion, which is deposited on the surface to thus form a thin 'film', which can protect the surface from corrosion.

Typical electroless plating solutions are described in Industrial Electro-Chemistry (2<sup>nd</sup> Edition, 1990, published by Chapman Hall, in particular pages 426-429 thereof) by Derek Pletcher and Frank Walsh.

The complexing agent is preferably EDDS, preferably present in a ratio to the metal ion to be reduced or to be deposited on the surface, of from 5:1 to 1:50.

It can be preferred that additional stabilizers are present to stabilise the sulfite-based bleach, such as additional complexing agents or builders.

#### Metal Scale Removal

The process of preparation of the aqueous compositions of the invention, comprising the step of addition of a complexing composition, comprising a complexing agent, to an aqueous solution, comprising calcium ions and one or more of the selected metal ions, can be part of a process for removal of scale containing one or more of the selected metal ions.

Thus, the aqueous solutions of the invention can also be used in a process for removal of metal scale, whereby (high quantities of) calcium ions are present, preferably from metal surfaces.

The metal scale removal process comprises the step of contacting the scale with an aqueous solution of the invention.

In a preferred process, the composition of the invention can be useful for removal of metal scale, which comprises one or more of the selected metal ions, from any (metal) surface which can be in contact with calcium ions, such as calcium ions contained in water.

For example, the process can be used for cleaning of industrial cooling systems or heating systems, such as boilers, which are of metallic nature, in particular of iron or steel nature, and which are in contact with calcium ions of the water-hardness, and which can rapidly form iron oxide deposits on the heat transfer surface. The formation of these deposits reduce the heat transfer efficiency. Therefore, the cleaning process of the invention can be useful to improve the efficiency of the cooling system

Most preferably the metal deposits to be removed or the metal surfaces to be cleaned are iron-, zinc-, aluminium- or copper-containing compounds, preferably salt or oxides of these metals. The preferred complexing agent is EDDS, as described herein.

It can be highly preferred that the compositions of the invention comprise a metal oxide, preferably zinc oxide, which can deposit onto the (metal) surfaces to prevent future scale formation, directly on these surface. It has been found that the complexing agent of the compositions can be useful to effectively deposit the metal oxide, preferably zinc oxide, onto the surface.

The precise amount of composition used in the process will depend on the nature of the process. Typically, the process requires the complexing agent to be present in an amount

of from at least 100 ppm, but more preferably from 0.001% to about 10%, preferably from about 0.01% to about 5% by weight of the composition.

It can be preferred that the aqueous composition of the invention, used in the metal-cleaning process, has a pH of at least 4, preferably of about 7 to 10.

The duration of the process, being the contact time of the aqueous solution with the metal surface is preferably from at least 30 seconds or more, but more preferably at least 10 minutes.

The aqueous composition of the present invention, used in the metal scale removal process, can contain additional builders or dispersants, as described herein, to remove additional or remaining deposits from the (metal) surfaces. Other additional ingredients of the compositions can be oxygen scavengers.

Depending on the nature of the cleaning-process, the aqueous composition can comprise an oxidising agent, which is capable of oxidising the metal ions to be removed, to thus facilitate the removal of the metal deposits in the oxidised form.

Typical oxidising agents which can be effectively employed include, but are not limited to, the alkali metal bromates, the alkali metal peroxides (the alkali metal perborates, potassium permanganate), hydrogen peroxide, air, oxygen, ozone, alkali metal and ammonium nitrites and mixtures thereof.

### Fermentation Processes

The process of preparation of the aqueous compositions of the invention, comprising the step of addition of a complexing composition, comprising a complexing agent, to an aqueous solution, comprising calcium ions and one or more of the selected metal ions, can be part of a fermentation process.

The aqueous composition of the invention can be used in fermentation processes, to improve the fermenting by yeast.

Namely, the presence of metal ions, such as one or more of the selected metal ions selected, can be detrimental to the performance of the yeast. As discussed above, it has been found that the presence of calcium ions can be essential for the performance of the yeast but that not all metal ions need to be removed from the yeast or yeast solution and that a selective complexing of the certain metal ions, in particular iron and copper, is required. This can be achieved with the compositions of the invention, which contain the specific selective complexing agents, which thus can prevent or reduce the detrimental effect of these metal ions on the yeast performance.

The fermentation process comprises the step of mixing the aqueous composition of the invention with a composition, comprising fermentable substances and yeast.

Preferred fermentation processes are processes for preparation of dairy products, in particular yoghurt, and alcoholic beverages, such as wine and beer.

It has been found that the use of the compositions of the invention, comprising the complexing agent, result in a reduced sensitivity of the wine or beer against discolouring, effect of temperature changes and exposure to air, resulting in an improved taste and colour of the wine.

In a preferred fermentation process for alcoholic beverages, the mixing step of the aqueous composition and the composition, comprising fermentable substances and yeast, takes place at the moment the yeast is added to the fermentable substances, e.g. the cooled wort, in the proper amount.

After the first 24 hours the fermentation is established and proceeds at an accelerated rate. The temperature of the fermenting wort increases and must thus be controlled to maintain yeast viability. Once the yeast has utilised the fermentable substances in the wort (usually after 7 to 10 days), the temperature is reduced and the yeast begins to settle. The yeast is precipitated and removed from the process mixture and then the complexing

agent and the metal ions can be removed from the process mixture, thereby clarifying the mixture.

An additional ingredient for use in the fermentation process, in particular for wine, can be an anti-oxidant or preservative, such as ascorbic acid.

Furthermore, in fermentation processes for alcoholic beverages, the use of these complexing agents has as an additional benefit that the clarification of the beverages is improved by an improved removal of the metal-fines.

#### Food Preparation Processes

The process of preparation of the aqueous compositions of the invention, comprising the step of addition of a complexing composition, comprising a complexing agent, to an aqueous solution, comprising calcium ions and one or more of the selected metal ions, can be part of a food preparation process, in particular of a food preservation process. Hereby, the complexing agent can serve as a anti-oxidant.

The aqueous composition of the invention is particularly useful in processes for preparation of lipid- or protein-containing products, such as oils, fats, meat and fish and egg-containing products. In particular, the composition is useful in processes for preparation of dairy products, which contain high levels of calcium.

In particularly suitable herein, is EDDS which has been found to be a very efficient, selective complexing agent in the presence of calcium, acting as a anti-oxidant or preservative, inhibiting free-radical formation and thereby preventing or reducing the oxidation of oxidation sensitive ingredients, e.g. reducing or preventing rancidity of the food product, thus improving the taste and appearance of the product.

The selected metal ions present in the process are in particular copper, cobalt or iron.



The precise amount of composition used in the process will depend on the nature of the process.

Additionally, the composition may comprises other commonly employed food-preservatives or antioxidants, such as ascorbic acid and citric acid or their salts; tocopherol; phosphates, nitrates.

### Tanning Processes

The process for preparation of the aqueous composition, comprising the step of addition of a complexing composition, comprising a complexing agent, to an aqueous solution, comprising calcium ions, can be part of a tanning process.

Thus, the aqueous composition of the invention can be used in tanning processes, in particular in processes for tanning of leather, or for artificial-tanning or self-tanning of the human skin.

The process can comprise any additional steps, commonly used in tanning processes and for example described in patent application EP245205.

The processes for tanning of leather can be tanning of (un-) treated, (unhaired) hides, or post-tanning or re-tanning of leather and comprises the step of contacting the leather or hides with the aqueous compositions of the invention.

In the tanning processes, one or more of the selected metal ions as described herein, are present to provide the tanning. The complexing agent of the aqueous compositions of the invention, is used in the tanning processes to selectively complex these metal ions and thereby to improve the tanning efficiency, thus permitting a reduction in the amount of tanning agent and metal ions required for the tanning of the leather, hides or skin.

Preferred metal ions used in tanning processes are zinc, chromium and iron or mixture thereof. In the process herein, these metal ions can be introduced in the aqueous

composition in the form of their salts, preferably sulfate, chloride or oxychloride salts, or can be (partially) comprised in the complexing agent. It can be preferred that an additional complexing agent and a chromium ion are present in the aqueous solutions of the invention, when used in such a tanning process.

It has been found that the compositions of the invention can improve the tanning process and that reduced levels of metal ions are required in the process, which has as an additional benefit that the amount of metal ions which is delivered to the environment, can be reduced.

The preferred complexing agent comprised in the compositions used in the tanning processes is EDDS in its salt or acid form.

Any tanning agent can be comprised in the aqueous compositions of the invention, when used in these processes. Preferably, the aqueous compositions of the invention, when used in the tanning process for tanning leather, comprises (a solution of) mineral tanning salts and/or synthetic tanning agents. This agent can comprise a salt of a synthetic, anionic aromatic tanning agent or its (anionic) precursor. Preferred can be a salt of sulphite or thiosulphite, a salt of a condensation-product of sulphonated phenol- or cresol and formaldehyde; a salt of a naphthalene sulphonic acid-formaldehyde condensation product; a salt of a formaldehyde condensation product of 4,4'-dihydroxydiphenylsulphonates with (hydroxy) arylsulphonic acids

The hides can be contacted with the tanning agent simultaneously with or after the aqueous composition is added to the hides.

Depending on the tanning agent and the metal ion used in the process, the aqueous solution can be acidified or alkalisied prior to contacting the hides. When firstly a mineral tanning salt is added to the process, alkalisising can be required preferably done by adding  $\text{Na}_2\text{SO}_3$ . When then secondly a synthetic tanning agent is used, the hides are

preferably neutralised before addition of this synthetic tanning agent to the composition of the process.

The amount of complexing agent and metal ions comprised in the aqueous compositions of the invention, will depend on the nature of the tanning processes. Typical amount of metal ions is from 0.005% to 5.0% by weight of the leather or hides to be tanned; and typical amount of complexing agents can be from 0.05% to 1.8% by weight of the leather or hides to be tanned.

Other additional components can be primary, secondary or tertiary amines, such as alkyl and alkenol amines.

When the tanning process is for re-tanning of leather, the process comprises the step of contacting the leather with the aqueous composition of the invention, which preferably comprises condensation products of sulphonated naphthalene with HCHO, and a neutralising agent, such as an amine compound.

The process can comprise the steps of contacting the hides with the aqueous solution of the invention and than storage of the hides and the composition. The aqueous composition can comprise tanning agents, but the compositions and the hides can also be stored prior to addition of the tanning agent.

Hereby, an additional benefit or advantage can be that the complexing agents comprised in the aqueous compositions can provide preservation of the hides or leather upon storage.

It can also be beneficial that the (part of) the complexing agent and optionally (part of) the selected metal ions are not removed from the treated leather during the process, because they have been found to prevent tanning-stain formation of the leather during use.

In processes of artificial-tanning or self-tanning of the human skin, the aqueous composition of the invention comprises the step of contacting the human skin with the aqueous composition.

It has been found that, when used in processes for self-tanning, the compositions of the invention are very effective in preventing skin damage.

The aqueous composition for use in artificial-tanning processes, can be in the form of a cosmetic cream, lotion, gel, or foam, and preferably in the form of an oil-in-water emulsion.

These compositions can comprise any additional ingredient commonly used in cosmetic compositions. Preferably, it comprises an additional sunscreen. Other preferred additional ingredients can be cetyl alcohol, stearyl alcohol, benzoate, octyl palmitate, dimethicone, polysorbate, glyceryl stearate, polyethylene glycol stearate, methyl glucose ether distearate, plant extracts, vitamins, Mg Al silicate, xanthan gum, glycerin, metabisulfite.

#### Dyeing Processes

The process of preparation of the aqueous compositions of the invention, comprising the step of addition of a complexing composition, comprising a complexing agent, to an aqueous solution, comprising calcium ions and one or more of the selected metal ions, can be part of a dyeing process.

Thus, the aqueous compositions of the invention can be used in dyeing processes, such as processes for dyeing of fabrics or textiles. In these processes, the complexing agents comprised in the composition can eliminate or reduce the negative impact of certain metal ions on the dyeing efficiency of the process. These metal ions, such as copper,

nickel, cobalt, chromium can be present in or on the fabric or can be present in the dyeing solution.

The dyeing process comprises the step of contacting the fabric with the aqueous composition. The aqueous composition can mixed with the dyeing solution or the dyestuff, prior to contacting the fabric. Alternatively, the fabric can be contacted with the composition, prior to addition of the dyeing solution or dyestuff.

The amount of composition or complexing agent therein will depend on the process conditions and the type of fabric which is to be dyed. In the dyeing process according to this invention, even small amounts of the compositions can be sufficient to obtain the benefits. In general, when the process comprises the step of mixing of the aqueous composition with the dyeing solution or dyestuff, around 0.005-5 g/ litre solution is required. The process can preferably be performed at about 10-200°C.

Examples of suitable process conditions are described in, for example, US patents 4,619,663; 3,539,445 and 4,339,236 which are incorporated herein by reference in their entireties.

Preferred dyes or dyestuffs can be diazo dyes, sulfide dyes, in particular, red disperse dye colour index 92, blue direct colour index 86, red reactive dye colour index 7, orange dye colour index 63, blue direct dye colour index 81, black direct dye colour index 71, green direct dye colour index 34, blue direct dye colour index 93, violet dye colour index 47.

A preferred complexing agent used in the compositions for use in the dyeing processes, is EDDS in the form of its acid or salt.

Optional further ingredients for use in the dyeing processes, can be further antifoams, dispersants, builders, wetting agents, binders and/or a dust inhibitors.

It has been found that the use of the compositions of the invention results in an more efficient, rapid and levelness dyeing, whereby the dye is more uniform applied to the fabric or textile.

### Treatment of Metal Poisoning

The aqueous compositions of the invention can be useful in or as compositions for treatment of metal poisoning. Thus, in accord with the invention, the complexing agents described herein, can be used for preparation of aqueous compositions for treatment of metal poisoning.

The metal poisoning of a human being or animal can be due to intake of metal ions from on external source, for example contaminated food or water, occupational exposure to metals, or it can be due to diseases which adversely affect the metal balance of the body, such as iron-loading. In particular, metal poisoning due to iron can be effectively treated with the compositions of the invention.

The complexing agents and the compositions comprising the agents are found to be highly selective for those metal ions, causing the poisoning, such as iron, in the presence of calcium ions, which are commonly present in the body in high quantities. Thus, it has been found that only very small amount of the compositions or complexing agents are required to obtain a very effective complexing or chelating of the metal ions causing the metal poisoning in the human body, and thus a very effective treatment.

The calcium ions and the selected metal ions can be present in the composition to be used, but are preferably present in the composition when in use.

The level of complexing agent used for preparation of the composition will depend on various factors, such as severity of the poisoning, the body weight of the patient and the method of treatment; if the treatment involves giving the composition be infusion over several hours, the level of complexing agent will generally be around 0.5-2 grams per 24 hours for children and 1-4 grams per 24 hours for adults.

The treatment of the patients can involve any steps which commonly can be used for administering medication, such as administering the composition of the invention by infusion or orally.

Depending on the method of treatment, the composition can comprise additional ingredients, as known in the art, such as carrier material, oil-in-water suspensions, additional vitamins such as vitamin C.

#### Polymerisation Processes

The process of preparation of the aqueous compositions of the invention, comprising the step of addition of a complexing composition, comprising a complexing agent, to an aqueous solution, comprising calcium ions and one or more of the selected metal ions, can be part of a polymerisation process.

Thus, the aqueous composition can be useful in polymerisation processes. The compositions have been found to improve the efficiency of the polymerisation process by catalysing the reaction and / or by stabilising the polymeric materials against hydrolysis.

For example, in a process for polymerisation of urethane, the hydrolytic stability of the formed polyurethanes is improved by use of the compositions of the invention.

For example in reduction processes for polymerisation of rubber the aqueous compositions of the invention are useful as redox catalyst or in the preparation step of the for redox catalysts.

#### Pesticidal or herbicidal or compositions: fungi, algae and plant growth inhibition, reduction or stabilisation compositions.

The process of preparation of the aqueous compositions of the invention, comprising the step of addition of a complexing composition, comprising a complexing agent and preferably one or more of the selected metal ions, to an aqueous solution, comprising

calcium ions, can be part of a process for inhibition, reduction or stabilisation of fungi, algae and/ or plant growth.

Furthermore, the complexing agents as defined herein, preferably EDDS, can be used for preparation of aqueous compositions, according to the invention, which are useful as herbicidal or fungicidal or algaecidal compositions for stabilisation, inhibition or reduction of algae, fungi and /or plant growth.

The calcium ions can be comprised in the composition to be used or can be present in the composition when in use.

The compositions, when used for preventing or inhibiting the growth of micro-organisms such as fungi, (aquatic) plants, algae, can be used in any application where such prevention or inhibition is required, such as in ponds, lakes, swimming pools and also be used for protecting e.g. wood, buildings, walls, paths, paint, adhesives, glue, paper, textiles, leather, plastics, cardboard, lubricants, cosmetics, food, caulking, feed and industrial cooling water.

Preferred metal ions are zinc ions, cobalt ions and in particular copper ions; a preferred complexing agent is EDDS, as described herein.

The aqueous composition can be obtainable by a process comprising the step of addition of a complex of a complexing agent and one or more of the selected metal ions, to an aqueous solution, comprising calcium ions.

Alternatively, the aqueous composition can be obtainable by a process comprising the step of addition of a complexing agent to a aqueous solution comprising one or of the selected metal ions, and calcium ions.

Preferably, a complex of the complexing agent and the selected metal ion is formed and subsequently added to the aqueous solution. To form such a complex, the complexing



agent is generally used in a weight ratio of 0.20 to 5 parts to one part of (the salt of) the selected metal ion(s).

The proportions of the complexing agents and the selected metal ions can vary within wide limits, depending on the application of the compositions. Generally, the (complexes of the) complexing agent and the selected metal ions will be used at a level of 1% to 90% by weight of the compositions, whereby 30% to 70% are preferred.

The composition can be applied in concentrated form or it can be diluted generally in the ratio of about 5 parts to 100 parts of water and the diluted solution is then applied, as described above.

A preferred copper-EDDS complex for use in the compositions can be prepared by mixing an aqueous solution containing a salt of EDDS and an aqueous solution containing copper sulphate, preferably a copper sulphate-triethanolamine complex.

Any additional ingredients useful in bactericide or herbicide compositions can be present in the compositions. Preferred additional ingredients can then be chlorides, such as calcium chlorides, chlorine -based bleaches, a buffer solution in water/ alcohol or alcohol esters, for example: NaCl, NH<sub>4</sub>Cl, Na<sub>2</sub>SO<sub>4</sub> and cetyl/oleic alcohol mono-ester in water.

Tertiary amines or (polymeric) quaternary ammonium salts can also be useful additional ingredients in the compositions of the invention when used for preventing or inhibiting the growth of fungi, algae or plants growth. A preferred compound can be dimethylbenzylammonium chloride.

Also other bactericidal or pesticidal or fungicidal agents can be present in the composition of the invention.

Other ingredients can be benzoyl acids or derivatives thereof, benzene or benzene derivatives, such as chlorobenzene, nitrilobenzene and benzene imidazol, and cyano-derivatives.

The compositions of the invention can be applied directly to the subject or environment or solution which needs protection from the of algae, plant, fungi growth or the elimination or reduction of the algae, plant, fungi growth, the compositions can be incorporated into another media, for example paints, agricultural sprays, and then applied to the subject or environment or solution which needs protection from the of algae, plant, fungi growth or the elimination or reduction of the algae, plant, fungi growth.

#### Plant Nutrients

The process of preparation of the aqueous compositions of the invention, comprising the step of addition of a complexing composition, comprising a complexing agent and one or more of the selected metal ions, to an aqueous solution, comprising calcium ions, can be part of a process for delivering plant nutrients to plants, in particular to improving the growth of the plants and to improve the development of chlorophylls in the plants.

Furthermore, the complexing agents as defined herein, preferably EDDS, can be used for preparation of aqueous compositions, according to the invention, which are useful as plant nutrient compositions for improvement of the plant growth.

A preferred metal ion present in the plant nutrient compositions can be iron.

The compositions can comprise additional ingredients, commonly employed in plant nutrient compositions.

The compositions can be applied to the plants by any known method, for example by foliar application or by spraying-on the composition on the roots of the plants.

#### Enzyme Activity Reduction

The aqueous compositions of the invention can be useful in or as compositions for reduction of the enzyme activity of enzymes, which require a metallic cofactor containing iron, copper, cobalt, zinc or nickel metal ions.

In a preferred aspect, the enzymes are in contact with the human or animal body.

The enzymes can be enzymes from bacteria's, fungi, algae, or from humans or animals.

In a highly preferred aspect of the invention, the compositions are used for reduction of the enzyme activity of enzymes present in the exudates, in particular esterase enzymes, including lipase enzymes.

Thus, in accord with the invention, the complexing agents described herein, can be used for preparation of aqueous compositions for reduction of the enzyme activity of these enzymes, in contact with the human or animal body or skin. The compositions comprise in use calcium ions, which can be present in the compositions and/ or in or on the human or animal body, and they comprise in use the selected metal ions.

In particular esterase enzymes, including lipase enzymes, are very effectively inhibited or inactivated by the compositions of the invention.

In a highly preferred aspect, the compositions are used for treatment of enzymatic dermatitis and/ or treatment of malodour of the body.

In preferred embodiments of the invention, the compositions comprising the complexing agents are useful for the treatment of enzymatic dermatitis or the treatment of formation of a malodour of the body, caused by enzymes, in particular for reduction of the enzyme activity of lipase enzymes.

The preferred complexing agent herein, is EDDS, as described above.

By treatment is meant herein an improvement of the affected condition of the human or animal body, caused by the enzyme activity. Thus includes in one preferred aspect of the invention, the reduction or at least stabilisation of the malodour of the body, which is caused by enzymes; in another preferred aspect of the invention, the reduction or at least stabilisation of the enzymatic dermatitis or the rash of the skin, caused by enzymes.

It is believed that the complexing agent selectively and effectively forms a complex with the present, selected metal ions, in particular copper and iron, which are required by the enzymes for their enzymatic activity, thereby reducing or inhibiting the enzymatic activity. Thus, for example, lipolytic enzymes, which can cause lipolytic dermatitis or which can catalyse the reactions for formation of fatty acids, which cause a malodour, can be inhibited, thus preventing, reducing a malodour of the body or skin rash.

The amount of the composition of the invention used for the reduction of the enzyme activity or in the treatment, will vary with the particular location of the condition being treated, the severity of the condition being treated, the expected duration of the treatment, any specific sensitivity to either the composition specific to the user, the condition of the user, concurrent therapies being administered, other conditions present in the user.

For the present invention it is preferred that a minimum inhibitory concentration of the compositions containing the complexing agent is, preferably topically, applied to act as a complexing agent for selected metal ions present on the skin, which are required by the enzymes for their enzymatic performance, in a form such that it is available to inhibit the activity of the enzymes present, in particular in the presence of calcium ions.

The complexing agents or compositions are in particular useful for the reduction of the enzyme activity of esterase enzymes, and thus for inhibition or inactivation of esterases, such as lipases or lipolytic enzymes. Their general activity is to hydrolyse fats present in the ester form (such as the glycerides found in human skin), and accordingly generate fatty acids and glycerol, which can cause irritation and malodour of the body. Because this group of enzymes is so widely distributed in plants, moulds, bacteria, milk, and

milk-products, as well as in almost all animal tissues, and because moreover human lipase enzymes are present in the pancreatic exudates, they are almost always present in or on the human or animal body.

The composition of the invention can be directly applied to the skin which is in contact with enzymes. Such compositions can be comprised in cosmetic composition, being in the form of a cream, lotion, foam, oil, ointment, powder or gel, which can be topically applied to the skin.

Highly preferred can be that the compositions are contained in a deodorant.

Alternatively, the compositions of the invention can be applied to an absorbent article, which can be brought in close contact with the skin which is in contact with the lipolytic enzymes. Such articles are preferably disposable articles such as diapers, incontinent pads, training pants, sanitary towels, feminine hygiene garments, dry or wet wipes.

The compositions can be prepared by any method known in the art for preparation for cosmetic compositions. The exact method will depend on the nature of the composition. The complexing agent can be added to the compositions in its acid or salt form, or be combined with other ingredients commonly used in cosmetic compositions, or dispersed or dissolved in water or oil or a water-in-oil emulsion prior to addition to the composition.

#### Nickel or Copper Dermatitis

The aqueous compositions of the invention can be useful in or as compositions for treatment of metal dermatitis, in particular nickel or copper dermatitis. Thus, in accord with the invention, the complexing agents described herein, can be used for preparation of aqueous compositions for treatment of metal dermatitis, in particular nickel or copper dermatitis.

The calcium ions can be comprised in the composition to be used or can be present in the composition when in use.

The preferred complexing agent herein, is EDDS, as described above.

The compositions can be prepared by any method known in the art for preparation for cosmetic compositions. The exact method will depend on the nature of the composition. The complexing agent can be added to the compositions in its acid or salt form, or be combined with other ingredients commonly used in cosmetic compositions, or dispersed or dissolved in water or oil or a water-in-oil emulsion prior to addition to the composition.

The composition can be applied directly to the skin or hair, which will be in contact with, or the vicinity of the metals or metal ions., which can be topically applied to the skin.

The compositions can also be applied (firstly) to an article, such as a wipe or tissue, which will then be applied to the skin.

The compositions of the invention can also be applied to a metal surface, which will be brought in the vicinity or contact with the skin or hair.

The required, effective amount of the composition will vary with the particular location of the condition being treated, the severity of the condition being treated, the expected duration of the treatment, any specific sensitivity to either the composition itself, or the concentration of the complexing agent to the user, the condition of the user, concurrent therapies being administered, other conditions present in the user.

The composition can comprise additional ingredients. Which ingredients are present and at which level depends on the character of the composition and the use thereof. Thus for example lotions will generally comprise different additional ingredients to powders.

It can be preferred that the compositions comprise one or more other ingredient which can reduce the metal dermatitis. Preferred can be the use of certain polymeric compounds,

such as a polyoxyethylene-polyoxypropylene copolymer (Pluronic® gel), polyethylene glycols, polyurethanes, synthetic carbopol polymers, compounds which can help the healing of the skin, such as vitamins (vitamin E) and cortisone's, and also compounds to soften the skin such as vaseline, glycerin, triethyleneglycol, lanolin, paraffin and another group of polymers extensively employed by pharmaceutical and cosmetic manufactures.

The compositions can be used for any suitable purpose. In particular, the present compositions are suitable for topical application to the skin or hair. In particular, the skin care compositions can be in the form of creams, lotions, gels, and the like. Preferably the cosmetic compositions herein are in the form of an oil-in-water emulsion of one or more oil phases in an aqueous continuous phase, each oil phase comprising a single oily component or a mixture of oily components in miscible or homogeneous form but said different oil phases containing different materials or combinations of materials from each other. The overall level of oil phase components in the compositions of the invention is preferably from about 0.1% to about 60%, preferably from about 1% to about 30% and more preferably from about 1% to about 10% by weight.

Claims

1. An aqueous composition, comprising calcium ions and one or more metal ions selected from the group consisting of Cu, Fe, Zn, Ni and Co and comprising a complexing agent, whereby the  $-\log_{10}C_T$  is equal to or greater than the smallest value of A or B, wherein

$$A \text{ is } -\log_{10}(L_T - M_T) \text{ and } B \text{ is } K_1(1 - K_2\sqrt{I})(1 - K_3.\exp(-K_4.P)),$$

wherein  $C_T$  is the total concentration of calcium ions,  $L_T$  is the total concentration of complexing agent,  $M_T$  is the total concentration of the metal ions, selected from the group consisting of Cu, Fe, Zn, Ni and Co; P is the pH of the composition, I is the ionic strength of the composition, whereby all concentrations are in moles/ litre, and where  $K_1$ ,  $K_2$ ,  $K_3$  and  $K_4$  are the following constants for the metals ions:

	Cu <sup>++</sup>	Fe <sup>+++</sup>	Zn <sup>++</sup>	Ni <sup>++</sup>	Co <sup>++</sup>
K1	11.062	5.754	7.963	13.098	7.642
K2	0.496	0.479	0.619	0.535	0.652
K3	2.479	9385. 0	24.20 2	1.473	32.069
K4	0.227	1.092	0.506	0.126	0.532

2. An aqueous composition according to claim 1, obtainable by a process comprising the step of addition of a complexing composition comprising a complexing agent and optional additional components to an aqueous solution comprising calcium ions.
3. An aqueous composition obtainable by a process according to claim 2, whereby the complexing composition, comprises one or more of the metal ions selected from the group consisting of Cu, Fe, Zn, Ni and Co, preferably in the form of a complex with the complexing agent.



4. An aqueous composition obtainable by a process according to claim 2 whereby the aqueous solution comprises one or more of the metal ions selected from the group consisting of Cu, Fe, Zn, Ni and Co.
5. An aqueous composition according to any preceding claim whereby the pH of the composition is at least 4 when the composition comprises copper or nickel ions, at least 7 when the composition comprises cobalt or zinc ions or at least 9.5 when the composition comprises iron ions.
6. An aqueous composition according to any preceding claim, whereby the complexing agent is an isomer of EDDS or a racemic mixture of the isomers of EDDS.
7. An aqueous composition according to any preceding claim which is not a composition for use in laundry or dish washing processes or for use in photography or photo-development processes.
8. A process according to claim 2 or 4 which is one or more steps in a reductive bleaching process.
9. A process according to claim 8 for reductive bleaching of cellulosic material, such as cotton, pulp or paper, wherein the aqueous composition comprises a sulfite-based reductive bleaching agent.
10. A process according to any of claims 2 to 4 which is one or more steps in a process for removal of metal scale.
11. A process according to any of claim 2 or 3 which is one or more steps in a process for electroless plating of metal.

12. A process according to claim 2 or 4 which is one or more steps in a fermentation process, preferably part of a process for clarification of beer or wine.
13. A process according to any of claims 2 to 4 which is one or more steps in a process for tanning of leather or human skin.
14. A process according to claim 2 or 3 which is one or more steps in a process for stabilisation or inhibition of algae, fungi or plant growth.
15. A process according to claim 2 or 4 which is one or more steps in a process for production or preservation of food.
16. Use of a complexing agent for preparation of an aqueous composition according to any of claims 1 to 7, for treatment of metal dermatitis of the external skin, preferably of copper or nickel dermatitis.
17. A process according to claims 2 or 4 which is one or more steps of a process for reduction of the enzymatic activity of enzymes in contact with the human or animal body or skin, preferably lipase enzymes present in the body extrudates.
18. Use of a complexing agent for preparation of an aqueous composition according to any of claims 1 to 7, for use in a process for reduction of the enzymatic activity of enzymes, in contact with the human or animal body, preferably lipase enzymes present in the body extrudates, preferably for treatment of enzymatic dermatitis or of malodour of the body.
19. Use of a complexing agent for preparation of an aqueous composition according to any of claims 1 to 7, for treatment of metal poisoning, preferably iron-loading.

20. Use of a complexing agent for preparation of an aqueous composition according to of claims 1 to 7, for stabilisation or inhibition or reduction of algae, fungi and/or plant growth.
21. Use of a complexing agent for complexing or chelating of one or more metal ions, selected from the group consisting of Cu, Fe, Zn, Ni and Co, in an aqueous composition whereby the  $-\log_{10}C_T$  is equal to or greater than the smallest value of A or B, wherein

$$A \text{ is } -\log_{10}(L_T - M_T) \text{ and } B \text{ is } K_1(1 - K_2\sqrt{I})(1 - K_3 \cdot \exp(-K_4 \cdot P)),$$

wherein  $C_T$  is the total concentration of calcium ions,  $L_T$  is the total concentration of complexing agent,  $M_T$  is the total concentration of the metal ions, selected from the group consisting of Cu, Fe, Zn, Ni and Co; P is the pH of the composition, I is the ionic strength of the composition, whereby all concentrations are in moles/ litre, and where  $K_1$ ,  $K_2$ ,  $K_3$  and  $K_4$  are the following constants for the metals ions:

	$\text{Cu}^{++}$	$\text{Fe}^{+++}$	$\text{Zn}^{++}$	$\text{Ni}^{++}$	$\text{Co}^{++}$
K1	11.062	5.754	7.963	13.098	7.642
K2	0.496	0.479	0.619	0.535	0.652
K3	2.479	9385.0	24.202	1.473	32.069
K4	0.227	1.092	0.506	0.126	0.532

22. Use of a complexing agent for preparation of an aqueous composition according to of claims 1 to 7 for delivering of Cu, Fe, Zn, Ni and/or Co metal ions to the human or animal body or to plants, preferably for delivery to plants, of plant nutrients comprising one or more of the said metal ions.

## INTERNATIONAL SEARCH REPORT

 International Application No.  
 PCT/IB 99/00122

## A. CLASSIFICATION OF SUBJECT MATTER

 IPC 6 D21C9/10 A61K31/195 C23C18/40 C14C3/00 C05D9/02  
 C05G3/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 D21C A61K C14C C05D C05G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 28464 A (DOW CHEMICAL CO) 8 December 1994 see page 2, line 22 - line 24 see claims; examples ---	1-11, 14, 20-22
A	DE 196 30 278 A (BASF AG) 29 January 1998 see the whole document ---	1-9, 21
A	WO 97 08288 A (DOW CHEMICAL CO) 6 March 1997 see page 9 ---	1-6, 14, 15, 17, 18, 21, 22
-/--		

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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## INTERNATIONAL SEARCH REPORT

International Application No.

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE WPI Section Ch. Week 8111 Derwent Publications Ltd., London, GB; Class E14, AN 81-18831D XP002103125 & SU 734 194 B (AS URALS CHEM INST) . 18 May 1980 see abstract -----	1-4, 7, 16-19, 21, 22
P, A	"EFFECTIVE AND SPECIFIC CHELATION IN THE PRESENCE OF CALCIUM IONS" RESEARCH DISCLOSURE, vol. 133, no. 407, 1 March 1998, page 241 XP000773859 see the whole document -----	1-22

## INTERNATIONAL SEARCH REPORT

Information on patent family members

Int: tional Application No

PCT/IB 99/00122

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9428464 A	08-12-1994	CA 2160701 A	08-12-1994
		CA 2180682 A	21-11-1994
		DE 4493718 T	22-08-1996
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		EP 0850293 A	01-07-1998



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US99/10067 <b>(22) International Filing Date:</b> 7 May 1999 (07.05.99)  <b>(30) Priority Data:</b> 09/074,432 7 May 1998 (07.05.98) US  <b>(71) Applicant:</b> THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US).  <b>(72) Inventors:</b> RUEBUSCH, Nicholas, Arthur; 14 West Kimberly Drive, Fort Thomas, KY 41075 (US). SMITH, Scott, Ed- ward; 3992 School Section Road, Cincinnati, OH 45211 (US). SWAILE, David, Frederick; 2797 Ridgewood Ave- nue, Cincinnati, OH 45213 (US).  <b>(74) Agents:</b> REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217-1087 (US).		<b>(81) Designated States:</b> BR, CA, CN, JP, MX. European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.          Before the expiration of the time limit for amending the          claims and to be republished in the event of the receipt of          amendments.</i>
<b>(54) Title:</b> AEROSOL PACKAGE COMPOSITIONS CONTAINING FLUORINATED HYDROCARBON PROPELLANTS		
<b>(57) Abstract</b> <p>Disclosed are anhydrous aerosol package compositions which comprise (a) a Lewis acid having a pKa of less than about 5.0; (b) from about 5 % to about 95 % by weight of a fluorinated hydrocarbon propellant; (c) a hydrogen bonded water source; and (d) a rust inhibition means. The aerosol package compositions are preferably anhydrous aerosol antiperspirants which comprise an antiperspirant active, a fluorinated hydrocarbon propellant such as 1,1-difluoroethane, and a rust inhibition means, wherein the antiperspirant active acts as a Lewis acid and contains hydrogen bonded water. It was found that aerosol package compositions containing fluorinated hydrocarbons, a strong Lewis acid, and a hydrogen bonded water source are surprisingly susceptible to corrosion or rust formation of any metal surface within the package, unless a known or otherwise effective rust inhibition means is added to or used in association with the packaged aerosol composition.</p>		

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**AEROSOL PACKAGE COMPOSITIONS CONTAINING  
FLUORINATED HYDROCARBON PROPELLANTS**

**TECHNICAL FIELD**

The present invention relates to aerosol package compositions which comprise a Lewis acid, a fluorinated hydrocarbon propellant, and means for inhibiting corrosion or rust of the aerosol package when the composition is packaged in a metal aerosol container.

**BACKGROUND OF THE INVENTION**

Packaged aerosol compositions are well known for use in a variety of consumer product areas, including application of personal care products such as hairsprays, hairstyling or conditioning gels or mousses, cosmetics, antiperspirants and deodorants, aftershave or shaving gels and creams, first aid sprays, and so forth. Other consumer product areas include household, industrial, or agricultural application.

All such aerosol products typically contain an active ingredient, a liquid carrier for the active ingredient, and a suitable propellant. The propellant is in the form of a compressed gas, typically a liquefiable gas, which acts to expel the liquid carrier and active ingredient from the aerosol package to the site of application. Examples of aerosol propellants include halogenated hydrocarbons such as fluorohydrocarbons and chlorofluorohydrocarbons, hydrocarbon gases such as butane and propane and dimethyl ethane, carbon dioxide, and nitrous oxide, and many others.

The use of many of these propellants, however, has been restricted for environmental or other safety concerns. The use of chlorofluorocarbons, for example, has been limited due to concerns that it contributes to depletion of the ozone layer of the upper atmosphere. By contrast, hydrocarbon propellants are not believed to be associated with ozone layer depletion and are now used extensively in aerosolized consumer products. Even the use of these hydrocarbon propellants, as well as other volatile organic compounds (VOC), are now being limited due to safety concerns associated with the release of large amounts of VOC's into the atmosphere from aerosolized consumer products.

Recently, fluorinated hydrocarbon propellants such as 1,1-difluoroethane have been used as a replacement for the more commonly used hydrocarbon propellants. It is believed that these fluorinated hydrocarbons are less harmful to the environment than most hydrocarbon propellants, and that the use of these fluorinated hydrocarbons allows for the formulation of aerosol products with reduced VOC content. These fluorinated hydrocarbons are especially useful in anhydrous antiperspirant and hairspray compositions. It has been found, however, that the use of these fluorinated hydrocarbon propellants can result in corrosion of the metal liner or surface within the aerosol container containing the propellant even when the composition is an anhydrous system that would not otherwise promote such corrosion. It has been found that corrosion of the metal aerosol container results in the visible appearance of rust on the inner surface of the container, which was very surprising given that the rust was first identified in a completely anhydrous system, and also given that comparable compositions containing hydrocarbon propellants do not have the same rust or corrosion problem.

It has also been discovered that this surprising rust or corrosion problem occurs in anhydrous systems when the fluorinated hydrocarbon is used in the presence of a strong Lewis acid having a  $pK_a$  of less than about 5.0 and a source of hydrogen bonded water (i.e. bound water). For antiperspirant compositions, the aluminum and/or zirconium polymer salt acts as a strong Lewis acid that also contains hydrogen bonded water. It has been found, quite surprisingly, that when fluorinated hydrocarbon propellants are used in such antiperspirant compositions that some rust formation can be noted on the inner surface of many of the metal aerosol packages containing such compositions.

It has now been discovered that this surprising rust formation problem in anhydrous aerosol compositions as described herein can be corrected by any known or otherwise effective rust inhibition means suitable for use in aerosol containers and suitable for use in consumer products.

In view of the foregoing, it is therefore an object of the present invention to provide an aerosol package composition containing fluorinated hydrocarbons which do not provide for canister corrosion or rust formation. It is yet another object of the present invention to provide an anhydrous aerosol package composition which contains a fluorinated hydrocarbon, a Lewis acid, and a source of hydrogen bonded water, wherein the components of the composition do not react and cause canister corrosion or rust formation. It is yet another object of the present invention to provide an anhydrous aerosol antiperspirant package composition which contains fluorinated hydrocarbons and an aluminum and/or zirconium polymer salt, that do not react and result in the corrosion of a metal aerosol container. It is yet another object of the present invention to provide

an anhydrous aerosol package composition wherein the inner surface of the aerosol container has been treated with a rust inhibitive material.

### **SUMMARY OF THE INVENTION**

The present invention is directed to aerosol package compositions which comprise (a) a Lewis acid having a pKa of less than about 5.0; (b) from about 5% to about 95% by weight of a fluorinated hydrocarbon propellant; (c) a hydrogen bonded water source; and (d) a rust inhibition means.

The present invention is also directed to aerosol antiperspirant package compositions which comprise (a) from about 0.5% to about 60% by weight of an antiperspirant active; (b) from about 5% to about 95% by weight of a fluorinated hydrocarbon propellant; and (c) a rust inhibition means.

It has been found that the use of fluorinated hydrocarbon propellants in aerosol package compositions containing an active ingredient can result in corrosion of the aerosol container when within the container are a strong Lewis acid and a bound water source.

### **DETAILED DESCRIPTION OF THE INVENTION**

The aerosol package compositions of the present invention are anhydrous systems which comprise a Lewis acid, a fluorinated hydrocarbon propellant, and a means for inhibiting corrosion of the aerosol package when the composition is packaged into a metal aerosol container.

The term "ambient conditions" as used herein refers to surrounding conditions at about one atmosphere of pressure, about 50% relative humidity, and about 25°C.

All percentages, parts and ratios as used herein are by weight of the total composition, unless otherwise specified. All such weights as they pertain to listed ingredients are based on the active level and, therefore, do not include solvents or by-products that may be included in commercially available materials, unless otherwise specified.

The aerosol package compositions of the present invention can comprise, consist of, or consist essentially of the essential elements and limitations of the invention described herein, as well as any of the additional or optional ingredients, components, or limitations described herein.

### Lewis Acid

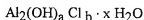
The aerosol package compositions of the present invention comprise a Lewis acid having a pKa value of less than about 5.0, preferably less than about 4.5. These Lewis acids for use in the composition are relatively strong acids and are those which are capable of interacting with the hydrogen bonded water component of the aerosol composition to result in the formation of a hydrated metal ion complex.

The aerosol package compositions of the present invention comprise the Lewis acid at any of a variety of concentrations depending upon the desired product form, the chemical and physical nature of the Lewis acid, the other formulation ingredients, and so forth. The concentration of most Lewis acids will typically range from about 0.5% to about 90%, preferably from about 5% to about 60%, more preferably from about 5% to about 35%, by weight of the composition. The Lewis acid is preferably included in the composition as a hydrated metal ion complex wherein the weight percentage of the metal complex is calculated on an anhydrous metal salt basis exclusive of water and any complexing agents such as glycine, glycine salts, or other complexing agents. Most preferred are Lewis acids in the form of antiperspirant zirconium and/or aluminum salts having hydrogen bonded water.

It has been found that strong Lewis acids for use in the anhydrous aerosol package compositions can react with a fluorinated hydrocarbon propellant in the presence of hydrogen bonded water, even though the composition still contains no free or unbound water, and result in canister corrosion when the aerosol package is a metal aerosol container. This interaction of a strong Lewis acid with the propellant can occur when the Lewis acid is included in the composition as a hydrated metal ion complex or when the Lewis acid is allowed to react with the propellant in the presence of another source of hydrogen bonded water, i.e. bound water.

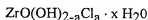
The strong Lewis acid for use in the aerosol package compositions include any compound, composition or other material that can be identified as a Lewis acid, provided that the Lewis acid is sufficiently strong and has a pKa value of less than about 5.0. These strong Lewis acids are capable of reacting with water and forming a hydrated metal ion complex, e.g., aluminum and/or zirconium antiperspirant salts. Preferably, the strong Lewis acid is present in the form of an antiperspirant active, nonlimiting examples of which include the astringent metallic salts, especially the inorganic and organic salts of aluminum, zirconium and zinc, as well as mixtures thereof. Particularly preferred are the aluminum and zirconium salts, such as aluminum halides, aluminum chlorohydrate, aluminum hydroxyhalides, zirconyl oxyhalides, zirconyl hydroxyhalides, and mixtures thereof.

Preferred aluminum salts for use in the aerosol package compositions, which also represent a strong Lewis acid and a hydrogen bonded water source as defined herein, include those which conform to the formula:



wherein a is from about 2 to about 5; the sum of a and b is about 6; x is from about 1 to about 6; and wherein a, b, and x may have non-integer values. Particularly preferred are the aluminum chlorhydroxides referred to as "5/6 basic chlorhydroxide", wherein a = 5, and "2/3 basic chlorhydroxide", wherein a = 4. Processes for preparing aluminum salts are disclosed in U.S. Patent 3,887,692, Gilman, issued June 3, 1975; U.S. Patent 3,904,741, Jones et al., issued September 9, 1975; U.S. Patent 4,359,456, Gosling et al., issued November 16, 1982; and British Patent Specification 2,048,229, Fitzgerald et al., published December 10, 1980, all of which are incorporated herein by reference. Mixtures of aluminum salts are described in British Patent Specification 1,347,950, Shin et al., published February 27, 1974, which description is also incorporated herein by reference.

Preferred zirconium salts for use in the aerosol package compositions, which also represent a strong Lewis acid and a hydrogen bonded water source as defined herein, include those which conform to the formula:



wherein a is from about 0 to about 2; x is from about 1 to about 7; and wherein a and x may both have non-integer values. These zirconium salts are described in Belgian Patent 825,146, Schmitz, issued August 4, 1975, which description is incorporated herein by reference. Particularly preferred zirconium salts are those complexes which additionally contain aluminum and glycine, commonly known as ZAG complexes. These ZAG complexes contain aluminum chlorhydroxide and zirconyl hydroxy chloride conforming to the above described formulas. Such ZAG complexes are described in U.S. Patent 3,679,068, Luedders et al., issued February 12, 1974; Great Britain Patent Application 2,144,992, Callaghan et al., published March 20, 1985; and U.S. Patent 4,120,948, Shelton, issued October 17, 1978, all of which are incorporated herein by reference.

Concentration of the preferred zirconiums and/or aluminum salts in the composition preferably range from about 0.5% to about 60%, more preferably from about 5% to about 26%, even more preferably from about 9% to about 15%, by weight of the composition. Aluminum salts are most preferred.

### **Propellant**

The aerosol package compositions of the present invention comprise a fluorinated hydrocarbon propellant that may react with the strong Lewis acid in the presence of hydrogen bonded water as described hereinabove. This interaction of the fluorinated propellant, strong Lewis acid, and hydrogen bonded water is believed to ultimately result in the formation of rust on any metal surface within the aerosol package.

The total concentration of the fluorinated hydrocarbon propellant, or the total concentration of any propellant combination comprising fluorinated hydrocarbon propellant, in the aerosol package composition can include one or more fluorinated hydrocarbon propellants, the total propellant concentration typically ranging from about 5% to about 95%, preferably from about 15% to about 60%, more preferably from about 40% to about 60%, by weight of the composition. The preferred fluorinated hydrocarbon propellant is 1,1-difluoroethane (Hydrofluorocarbon 152A) supplied as Dymel 152A by Dupont.

The aerosol package composition may further comprise other aerosol propellants for use in combination with the fluorinated hydrocarbon propellant described herein. Suitable optional propellants include any propellant that is known or otherwise effective for use in consumer aerosol products, and which is otherwise compatible with the essential and any optional ingredients in the aerosol composition. Nonlimiting examples of optional propellants include hydrocarbon propellants such as propane, butane, dimethyl ether, and isobutane, nitrous oxide, carbon dioxide, and other halogenated hydrocarbons such as trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethane, trichlorotrifluoroethane, trichlorotetrafluoroethane, monochlorodifluoromethane, and mixtures thereof.

### **Rust Inhibition Means**

The aerosol package compositions of the present invention comprise a means for inhibiting corrosion or rust of any metal surface or liner within the aerosol container. The rust inhibition means includes any known or otherwise effective means for controlling or eliminating the formation of rust or corrosion on metal surfaces within an aerosol or other metal-containing package or surface.

Preferred rust inhibition means are those which can control or prevent the interaction of the Lewis acid, fluorinated hydrocarbon propellant, and hydrogen bonded water to thus inhibit the formation of any corrosive material from such an interaction, or otherwise inhibit the formation of conditions that promote corrosion of any metal surface or liner within the aerosol container. Also preferred are any known or otherwise effective

rust inhibition means in the form of a chemical or physical barrier that prevents or minimizes contact between any metal surface within the aerosol package and the aerosol composition contained therein.

Preferred rust inhibition means include 1) the use of inhibitors that minimize the interaction of the Lewis acid, the fluorinated hydrocarbon propellant, and hydrogen bonded water, 2) the use of scavenging and/or sequestering agents to effectively bind, neutralize or otherwise inactivate any corrosive materials resulting from the interaction of the Lewis acid, fluorinated hydrocarbon propellant, and hydrogen bonded water. Less preferred are those rust inhibition means that provide a chemical or physical barrier between the interacting materials and any metal surface within the aerosol package, an example of which involves the treatment of the metal surfaces within the package with a rust inhibitive material to provide a barrier between the inner surface and the corrosive material.

Nonlimiting examples of rust inhibition means which minimize the interaction of the Lewis acid, fluorinated hydrocarbon, and hydrogen bonded water include the use of a water-soluble barrier that interacts with and coats the Lewis acid, coating the Lewis acid with a water-insoluble polar solvent, and the use of a solvent in the aerosol composition that is immiscible with the fluorinated hydrocarbon propellant. Suitable nonlimiting examples of water-soluble barriers for interaction with and coating of the Lewis acid include materials such as lecithin, carbohydrates, dextrin, and mixtures thereof. Specific nonlimiting examples of suitable water-insoluble polar solvents for interaction with and coating of the Lewis acid include compounds such as butyl stearate, isopropyl palmitate, dimethicone copolyol, and mixtures thereof. Suitable nonlimiting examples of solvents that are immiscible with the fluorinated hydrocarbon propellant and that can be added to the aerosol composition include mineral oil, polydecene, and similar other materials. Particularly preferred is the use of solvents that are immiscible with the fluorinated hydrocarbon propellant.

Examples of rust inhibition means that effectively bind, neutralize or otherwise inactivate any corrosive materials resulting from the interaction of the Lewis acid, fluorinated hydrocarbon propellant, and hydrogen bonded water, include the use of any known or otherwise effective fluoride scavenging agent such as calcium chloride, calcium carbonate, and mixtures thereof. Examples of suitable sequestering agents include any known or otherwise effective material for chelating fluoride or other similar cation, some examples of which include chelating amines such as ethylene diamine-N,N,N',N'-tetracetic acid (EDTA), acetylacetone, nitrilotriacetic acid, oxalate, citric acid, 1,2-diaminocyclohexane-N,N,N',N'-tetracetic acid, 4,5-dihydroxybenzene-1,3-disulfonic acid,

pyrocatechol-3,5-disulfonate, salicylic acid, 5-sulfosalicylic acid, xylenol orange, aurintricarboxylic acid, 2,2'-pyridyl ethylene diamine, glycine, 8-hydroxyquinoline-5-sulfonic acid, lactic acid, 1,10-phenanthroline, pyridine, pyridine-2,6-dicarboxylic acid, 8-quinolinol, succinic acid, tartaric acid, thioglycolic acid, 1,1,1-trifluoro-3,2'-thenylacetone, triethylene tetramine, and mixtures thereof.

Alternatively, the inner surface of any metal within the aerosol package, typically the inner metal surface or liner within the aerosol package, can be treated or coated with any material suitable for preventing or minimizing contact between such metal surface and any potentially corrosive material or combination of materials within the aerosol composition. Preferably, the inner surface of the aerosol package is impregnated or coated with rust inhibitive materials such as thermoplastic resins or other synthetic resin materials. Nonlimiting examples of suitable thermoplastic resins include polyethylene, polypropylene, a copolymer or modified resin of polyethylene and polypropylene, and mixtures thereof. Nonlimiting examples of other synthetic resin coating materials include polyester resin coatings, aminoalkyl resin coatings, amide resin coatings, imide resin coatings, acrylic resin coatings, phenolic resin coatings, vinyl chloride resin coatings, epoxy resin coatings, polyurethane resin coatings, silicone resin coatings, and mixtures of these coatings.

Other suitable means for providing a barrier between the aerosol metal surface and the contained composition includes increasing the tin plate coating weight of the inner metal surface to above about 2.4 grams/m<sup>2</sup> (grams of tin plating per inner surface area), preferably above about 2.8 to about 5.6 grams/m<sup>2</sup>.

#### **Hydrogen Bonded Water**

The aerosol package compositions of the present invention are anhydrous compositions that preferably comprise only hydrogen bonded water in an amount sufficient to promote interaction with the fluorinated hydrocarbon and Lewis acid components described herein. This hydrogen bonded water, also referred to herein as bound water, is typically present in relatively low concentrations and is in the form of water that is hydrogen bonded to the Lewis acid or other essential or optional material within the aerosol composition, or which is otherwise not free water. The term "hydrogen bonded water" as used herein therefore includes water that is hydrogen bonded to or otherwise trapped by a substrate, or which is otherwise not free water. Examples of materials containing hydrogen bonded water for use in the composition are antiperspirant actives such as aluminium and/or zirconium polymer salts.



The aerosol package compositions of the present invention are therefore anhydrous compositions which comprise little or no unbound or free water. In this context, the term "anhydrous" means that the aerosol composition of the present invention contains less than about 5%, preferably less than about 3%, more preferably less than about 1%, most preferably zero percent, by weight of unbound water. In this context, the term "unbound water" specifically excludes hydrogen bonded water as described herein, and therefore only includes free or unbound water within the composition.

The aerosol package composition most preferably contains zero percent by weight of unbound water. For those aerosol embodiments containing some but low water concentrations, i.e. above zero percent but less than about 5% by weight of water, it is highly preferred that the small amounts of unbound water have a relatively neutral pH to avoid reaction with the fluorinated hydrocarbon. This can be accomplished by a number of means including the use of buffering agents, barriers between the Lewis acid and the unbound water, and other means well known for use in controlling formulation pH values.

#### Optional Liquid Carrier

The aerosol package compositions of the present invention may further comprise an optional liquid carrier suitable for application to human hair or skin, preferably a hydrophobic liquid carrier. The liquid carrier may provide emolliency benefits, acts as a diluent for the strong Lewis acid component within the aerosol package composition, and facilitates the uniform distribution of any active ingredients or other materials within the composition onto the skin, e.g., antiperspirant active.

The optional liquid carrier can be included in the aerosol package compositions as an individual liquid carrier or a combination of liquid carriers, the total concentration of the liquid carrier typically ranging from about 15% to about 55%, preferably from about 20% to about 45%, more preferably from about 25% to about 35%, by weight of the composition.

The optional liquid carrier for use herein include volatile silicones, nonvolatile silicones, functionalized silicones, volatile organics, nonvolatile organics, and mixtures thereof. As used herein the term "volatile" refers to those liquid carrier materials which have a vapor pressure under ambient conditions of at least about 0.2 mm of Hg. Conversely, the term "nonvolatile" refers to those liquid carrier materials which have vapor pressure of less than about 0.2 mm of Hg under ambient conditions. The aerosol package composition preferably comprises a combination of volatile and nonvolatile silicone materials, more preferably a combination of volatile and nonvolatile silicone liquid

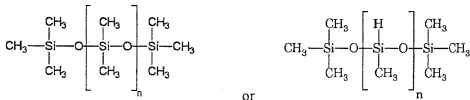
carriers, examples of which are described in U.S. Patent 5,156,834 (Beckmeyer et al.), which description is incorporated herein by reference.

Specific examples of suitable volatile silicone liquid carriers include cyclic, linear or branched chain silicones having the requisite volatility defined herein. Nonlimiting examples of suitable volatile silicones are described in Todd et al., "Volatile Silicone Fluids for Cosmetics", Cosmetics and Toiletries, 91:27-32 (1976), which descriptions are incorporated herein by reference. Preferred among these volatile silicones are the cyclic silicones having from about 3 to about 7, more preferably from about 4 to about 5, silicone atoms. Most preferably are those which conform to the formula:



wherein n is from about 3 to about 7, preferably from about 4 to about 5, most preferably 5. These volatile cyclic silicones generally have a viscosity value of less than about 10 centistokes. All viscosity values described herein are measured or determined under ambient conditions, unless otherwise specified. Suitable volatile silicones for use herein include, but are not limited to, Cyclomethicone D-5 (commercially available from G. E. Silicones); Dow Corning 344, and Dow Corning 345 (commercially available from Dow Corning Corp.); GE 7207, GE 7158 and Silicone Fluids SF-1202 and SF-1173 (available from General Electric Co.); SWS-03314, SWS-03400, F-222, F-223, F-250, F-251 (available from SWS Silicones Corp.); Volatile Silicones 7158, 7207, 7349 (available from Union Carbide); Masil SF-V (available from Mazer); and combinations thereof.

Optional liquid carriers may also include a non-volatile silicone carrier other than or in addition to the volatile silicone carriers described hereinbefore. These non-volatile silicone carriers are preferably linear silicones which include, but are not limited to, those which conform to either of the formulas:



wherein n is greater than or equal to 1. These linear silicone materials will generally have viscosity values of up to about 100,000 centistoke, preferably less than about 500 centistoke, more preferably from about 1 centistoke to about 200 centistoke, even more

preferably from about 1 centistoke to about 50 centistoke, as measured under ambient conditions. Examples of non-volatile, linear silicones suitable for use in the aerosol compositions include, but are not limited to, Dow Corning 200, hexamethyldisiloxane, Rhodorsil Oils 70047 available from Rhone-Poulenc, Masil SF Fluid available from Mazer, Dow Corning 225, Dow Corning 1732, Dow Corning 5732, Dow Corning 5750 (available from Dow Corning Corp.); SF-96, SF-1066 and SF18(350) Silicone Fluids (available from G.E. Silicones); Velvasil and Viscasil (available from General Electric Co.); and Silicone L-45, Silicone L530, Silicone L-531 (available from Union Carbide), and Siloxane F-221 and Silicone Fluid SWS-101 (available from SWS Silicones).

Other optional liquid carriers include modified or organofunctional silicone carriers such as polyalkylsiloxanes, polyarylsiloxanes, polyestersiloxanes, polyethersiloxane copolymers, polyfluorosiloxanes, polyaminosiloxanes, and combinations thereof. These modified silicone carriers are typically liquid under ambient conditions, and have a preferred viscosity of less than about 100,000 centistokes, more preferably less than about 500 centistokes, even more preferably from about 1 centistoke to about 50 centistokes, and most more preferably from about 1 centistoke to about 20 centistokes. These modified silicone carriers are generally known in the chemical arts, some examples of which are described in 1 *Cosmetics, Science and Technology* 27-104 (M. Balsam and E. Sagarin ed. 1972); U.S. Patent 4,202,879, issued to Shelton on May 13, 1980; U.S. Patent 5,069,897, issued to Orr on December 3, 1991; which descriptions are incorporated herein by reference.

Other optional liquid carriers include volatile, non-polar organic solvents such as isohexadecane, isododecane, various other hydrocarbon oils, and combinations thereof. In this context, the term "nonpolar" refers to those solvents having a solubility parameter of less than  $8.0 \text{ (cal/cm}^3)^{0.5}$ , preferably from about  $5.0 \text{ (cal/cm}^3)^{0.5}$  to less than  $8.0 \text{ (cal/cm}^3)^{0.5}$ , more preferably from  $6.0 \text{ (cal/cm}^3)^{0.5}$  to about  $7.60 \text{ (cal/cm}^3)^{0.5}$ .

Suitable volatile nonpolar solvents are those solvents having the above-described vapor pressure and solubility parameters, which can also include hydrocarbons, esters, amides, and ethers having the requisite vapor pressure and solubility parameter. Preferred are nonpolar hydrocarbon solvents which can be cyclic, branched or chain configurations, most preferably branched chain hydrocarbons.

Preferred volatile nonpolar solvents are the branched chain hydrocarbons having the requisite vapor pressure and solubility parameter and having from about 4 to about 30 carbon atoms, preferably from about 4 to about 20 carbon atoms, more preferably from about 6 to about 20 carbon atoms. Specific nonlimiting examples of these nonpolar volatile solvents include the isoparaffins available from Exxon Chemical Company,

Baytown, Texas U.S.A. as Isopar M (C13-C14 isoparaffin), Isopar C (C7-C8 Isoparaffin), C8-C9 Isoparaffin (Isopar E), Isopar G (C10-11 Isoparaffin), Isopar L (C11-C13 Isoparaffin) and Isopar H (C11-C12 Isoparaffin). Other nonlimiting examples of suitable branched chain hydrocarbons include Permethyl 99A (isododecane), Permethyl 102A (isoeicosane), Permethyl 101A (isohexadecane), and combinations thereof. The Permethyl series are available from Preperse, Inc., South Plainfield, New Jersey, U.S.A. Other nonlimiting examples of suitable branched chain hydrocarbons include petroleum distillates such as those available from Phillips Chemical as Soltrol 130, Soltrol 170, and those available from Shell as Shell Sol 70, -71, and -2033, and combinations thereof.

Nonlimiting examples of other suitable nonpolar volatile solvents include dibutyl adipate, diisopropyladipate, dodecane, octane, decane and combinations thereof, and the Norpar series of paraffins available from Exxon Chemical Company as Norpar 12, -13, and -15. Yet another example includes C11-C15 alkanes/cycloalkanes available from Exxon as Exxsol D80.

Other optional liquid carriers include nonvolatile, polar organic solvents such as mono and polyhydric alcohols, fatty mono and polyhydric alcohols, fatty acids, esters of mono and dibasic carboxylic acids with mono and polyhydric alcohols, polyoxyethylenes, polyoxypropylenes, polyalkoxylates ethers of alcohols, and combinations thereof. Preferably such optional liquid carriers are water-immiscible liquids under ambient conditions. Specific nonlimiting examples of such solvents include propyleneglycol monoisostearate; PPG-3 myristyl ether; PEG-8; 1,2, pentanediol, PPG-14 butylether, dimethyl isosorbide, isopropyl myristate, ethyl laurate, isopropyl palmitate, isopropyl behenate, decyl acetate, behenyl butyrate, hexadecyl acetate, decyl decanoate, methyl oleate, lauryl laurate, dioctyladipate, and combinations thereof. Other suitable water-immiscible, polar organic liquid carriers or solvents for use herein are described in Cosmetics, Science, and Technology, Vol. 1, 27-104, edited by Balsam and Sagarin (1972); U.S. Patent 4,202,879 issued to Shelton on May 13, 1980; U.S. Patent 4,816,261 issued to Luebbe et al. on March 28, 1989; U.S. Patent 3,968,203 issued to Spitzer et al. on July 6, 1976; U.S. Patent 3,752,540 issued to Wahl on April 13, 1973; and U.S. Patent 3,959,459, issued to Curry on May 25, 1976, which descriptions are incorporated herein by reference.

#### Optional Suspending Agent

The aerosol package compositions of the present invention may further comprise a suspending or bulking agent to help suspend any dispersed solids or liquids within the composition which is most typically in liquid form. Suitable suspending agents include

any material known or otherwise effective in providing suspending or bulking properties to the composition, or which otherwise provide the desired viscosity to the final product form. These suspending agents include inorganic particulates such as clays or silicas, or combinations thereof.

Suitable optional suspending agents for use in the aerosol package composition include particulate suspending or thickening agents such as clays and colloidal pyrogenic silica pigments. Other known or otherwise effective particulate suspending agents can likewise be used in the aerosol package composition. Concentrations of optional particulate suspending agents preferably range from about 0.05% to about 3%, more preferably from about 0.2% to about 2%, even more preferably from about 0.5% to about 1%, by weight of the aerosol composition.

Suitable colloidal pyrogenic silica pigments include Cab-O-Sil®, a submicroscopic particulated pyrogenic silica. Silicas are not preferred for use herein but can be utilized at concentrations of from about 0.05% to about 3% by weight of the composition.

Suitable clay suspending agents include montmorillonite clays, examples of which include bentonites, hectorites, and colloidal magnesium aluminum silicates. These and other clay suspending agents are preferably hydrophobically treated, and when so treated will generally be used in combination with a clay activator. Non-limiting examples of suitable clay activators include propylene carbonate, ethanol, and combinations thereof. The amount of clay activator will typically range from about 25% to about 75%, more typically from about 40% to about 60%, by weight of the clay. Propylene carbonate is the preferred clay activator and is typically included in the composition at a weight ratio of suspending agent to activator of from about 1:0.33 to about 1:1.

Preferred optional clay suspending agents include hydrophobic bentonites available under the trade name Bentone®. Specific nonlimiting examples of suitable Bentones include Bentone 38, Bentone 34, Bentone 27, Bentone 14, Bentone LT, all of which have a particle size of below about 5 microns and are commercially available from NL Industries, Inc..

#### Other Optional Components

The aerosol package compositions of the present invention may further comprise other optional components known or otherwise effective for use in aerosolized antiperspirant or other personal care products, provided that the optional components are physically and chemically compatible with the essential component described herein, or do not otherwise unduly impair product stability, aesthetics or performance.

Nonlimiting examples of optional ingredients include preservatives, bactericides, perfumes, coloring agents, cosmetics, fillers, thickeners, allantoin, dyes, antisyneresis agents, wash-off aids, and other similar materials. The concentration of such optional ingredients generally ranges from about 0.01% to about 20% by weight of the composition.

The aerosol package composition may further comprise an active ingredient which may be added to or used in place of any antiperspirant active materials in the composition. Nonlimiting examples of such active ingredients include emollients, pharmaceutical actives, antifungal or other suitable antimicrobial agent, sun screens, deodorant perfumes, deodorant antimicrobials such as triclosan or triclocarban or other similar materials, and combinations thereof.

#### **Method of Manufacture**

The aerosol package compositions of the present invention may be prepared by any known or otherwise effective technique, suitable for making and formulating an aerosol package composition, provided that the composition also has a means for inhibiting corrosion or rust of any metal surface or liner within the aerosol container.

Methods for preparing the aerosol package compositions of the present invention include conventional formulation and mixing techniques for aerosol formulations. Suitable methods include the formation of an aerosol concentrate by dispersing a suspending agent and activator in a liquid carrier. The dispersion is stored until it thickens due to swelling of the suspending agent. For antiperspirant aerosols, the antiperspirant active is then added with mixing. The mixture is then homogenized by the use of a Gifford-Wood shearing type homogenizer until a gel is formed and the desired viscosity is obtained. The gel constitutes the aerosol concentrate. The aerosol concentrate is then packaged into a suitable container such as a metal aerosol container.

The aerosol composition of the present invention can be contained or dispensed in any known or otherwise effective aerosol container or delivery system. All such containers or delivery systems should be compatible with the essential and any selected optional ingredients of the aerosol composition of the present invention.

Preferably, the aerosol composition is packaged in a pressurized aerosol container by combining the aerosol concentrate with a fluorinated hydrocarbon propellant such as 1,1-difluoroethane at a concentrate:propellant weight ratio of from about 0.5:1 to about 2.3:1.

### EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention. All exemplified concentrations are weight-weight percents, unless otherwise specified.

#### Example 1

The composition described below is an anhydrous antiperspirant composition packaged within a metal aerosolized canister. The composition contains hydrogen bonded water associated with the antiperspirant active and contains no free or unbound water. The antiperspirant active acts as a strong Lewis acid that has both hydrogen bonded water and a pKa value of less than about 5.0. The aerosol package also contains a rust inhibition means in the form of a barrier surface or liner (epoxy-phenolic resin) within the aerosol package that prevents corrosion of the metal inner surface of the package.

#### Antiperspirant Concentrate

<u>INGREDIENT</u>	<u>WEIGHT %</u>
Dimethicone/Cyclomethicone Blend	53.937
Isopropyl Myristate	12.562
Quaternium-18 Hectorite	2.513
Aluminum Chlorohydrate	30.151
Propylene Carbonate	0.837

The concentrate is prepared by combining the dimethicone/cyclomethicone blend with isopropyl myristate. The clay and propylene carbonate are then added and dispersed into the mixture. The resultant dispersion is stored for 15 to 20 minutes until it thickens to the desired viscosity. The aluminum chlorohydrate (contains hydrogen bonded water) is then added with agitation. The resulting concentrate is homogenized in a Gifford-Wood shearing type homogenizer until a concentrate gel is formed having the desired viscosity. The homogenized concentrate is combined with 1,1-difluoroethane propellant at a concentrate to propellant weight ratio of about 0.66:1 in the epoxy-phenolic treated aerosol canister.

Examples 2-5

The compositions described below are aerosol antiperspirants that are packaged in a metal aerosol canister, and which contain a rust inhibition material which controls or prevents the development of rust or corrosion of the metal aerosol canister. The composition contains hydrogen bonded water associated with the antiperspirant active and contains no free or unbound water. The antiperspirant active acts as a strong Lewis acid that has both hydrogen bonded water and a pKa value of less than about 5.0. The aerosol compositions are formulated by conventional formulation and mixing techniques for making aerosol antiperspirant compositions.

Ingredient	Examples			
	2	3	4	5
Aluminum Chlorohydrate	12.00	12.00	12.00	12.00
Cyclomethicone D5	19.67	15.67	19.67	---
Butyl Stearate	---	---	---	21.67
Isopropyl Myristate	5.00	5.00	5.00	5.00
Quaternium 18 hectorite	1.00	1.00	1.00	1.00
Propylene Carbonate	0.33	0.33	0.33	0.33
Calcium Chloride Scavenging agent	---	---	2.00	---
EDTA Sequestering agent	2.00	---	---	---
Lechtin	---	6.000	---	---
1,1-difluoroethane	60.00	60.00	60.00	60.00



**WHAT IS CLAIMED IS:**

1. An anhydrous aerosol antiperspirant package composition comprising:
  - (a) from about 0.5% to about 60% by weight of an antiperspirant active;
  - (b) from about 5% to about 95% by weight of fluorinated hydrocarbon propellant; and
  - (c) a rust inhibition means.
2. The composition of Claim 1 wherein the composition contains zero percent by weight of free water and wherein the antiperspirant active contains hydrogen bonded water.
3. The composition of Claim 2 wherein the fluorinated hydrocarbon propellant is 1,1-difluoroethane.
4. The composition of Claim 3 wherein the antiperspirant active is selected from the group consisting of zirconium salt, aluminum salt, and combinations thereof.
5. The composition of Claim 4 wherein the rust inhibition means comprises a means for inhibiting the interaction between the antiperspirant active and 1,1-difluoroethane.
6. The composition of Claim 5 wherein the means for inhibiting the interaction of the antiperspirant active with 1,1-difluoroethane is selected from the group consisting of reacting the antiperspirant active with a water-soluble barrier, coating the antiperspirant active with a water-insoluble polar solvent, adding a solvent that is immiscible with 1,1-difluoroethane, and combinations thereof.
7. The composition of Claim 4 wherein the rust inhibition means comprises a scavenging agent for any corrosive material that forms within the composition.
8. The composition of Claim 4 wherein the rust inhibition means comprises a sequestering agent for any corrosive material that forms within the composition.
9. The composition of Claim 4 wherein the rust inhibition means comprises a barrier coating within the package composition which prevents contact between the composition and an inner metal surface of the aerosol package.

10. The composition of Claim 9 wherein the barrier coating is selected from the group consisting of polyethylene resins, polypropylene resins, copolymers of polyethylene resins, copolymers of polypropylene resins, polyester resins, aminoalkyl resins, acrylic resins, phenolic resins, amide resins, imide resins, vinyl chloride resins, epoxy resins, polyurethane resins, silicone resins, and mixtures thereof.
11. An anhydrous aerosol package composition comprising:
  - (a) a Lewis acid having a pKa of less than about 5.0;
  - (b) from about 5% to about 95% by weight of a fluorinated hydrocarbon propellant;
  - (c) a hydrogen bonded water source; and
  - (d) a rust inhibition means.
12. The composition of Claim 11 wherein the composition contains zero percent by weight of free water.
13. The composition of Claim 12 wherein the fluorinated hydrocarbon propellant is 1,1-difluoroethane.
14. The composition of Claim 11 wherein the Lewis acid has a pKa value of less than about 4.5.
15. The composition of Claim 12 wherein the rust inhibition means comprises a means for inhibiting the interaction between the Lewis acid, the hydrogen bonded water source, and the fluorinated hydrocarbon propellant.
16. The composition of Claim 15 wherein the means for inhibiting the interaction between the Lewis acid, the hydrogen bonded water source, and the fluorinated hydrocarbon propellant is selected from the group consisting of reacting the Lewis acid with a water-soluble barrier, coating the Lewis acid with a water-insoluble polar solvent, adding a solvent that is immiscible with the fluorinated hydrocarbon propellant, and combinations thereof.
17. The composition of Claim 12 wherein the rust inhibition means comprises a scavenging agent for any corrosive material that forms within the composition.

18. The composition of Claim 12 wherein the rust inhibition means comprises a sequestering agent for any corrosive material that forms within the composition.
19. The composition of Claim 12 wherein the rust inhibition means comprises a barrier coating within the package composition which prevents contact between the composition and an inner metal surface of the aerosol package.
20. The composition of Claim 19 wherein the coating barrier is selected from the group consisting of polyethylene resins, polypropylene resins, copolymers of polyethylene resins, copolymers of polypropylene resins, polyester resins, aminoalkyl resins, amide resins, imide resins, acrylic resins, phenolic resins, vinyl chloride resins, epoxy resins, polyeurathane resins, silicone resins, and mixtures thereof.
21. The composition of Claim 12 wherein aerosol package has an inner tin plate coating of at least about 2.4 grams/m<sup>2</sup>.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 99/10067

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K7/32 A61K7/00 A61K7/34 A61K7/38

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 534 861 A (WICKHEN PRODUCTS) 6 December 1978 (1978-12-06)  claims ---	1,2,4,6, 7,11,12, 15,16
X	US 3 725 540 A (WAHL, E. ) 3 April 1973 (1973-04-03)  claims; example 2 ---	1,2,4,6, 7,11,12, 15,16
X	GB 1 362 495 A (BLENDAX ) 7 August 1974 (1974-08-07) page 2, line 127-130; claims 1,2; example 1 ---	1,2,4,9, 10,19,20
X	GB 1 482 917 A (COLGATE-PALMOLIVE CO.) 17 August 1977 (1977-08-17) column 2-3; claims 1,4,5 -----	1-6, 11-16

☐ Further documents are listed in the continuation of box C

☒ Patent family members are listed in annex.

### \* Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

30 August 1999

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## INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No.

PCT/US 99/10067

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